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Is There a Future for Neuropeptide Receptor Ligands in the Treatment of Anxiety Disorders?

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ABSTRACT. This review provides an overview of preclinical and clinical evidence of a role for the neuroactive peptides cholecystokinin (CCK), corticotropin-releasing factor (CRF), neuropeptide Y (NPY), tachykinins (i.e., substance P, neurokinin [NK] A and B), and natriuretic peptides in anxiety and/or stress-related disorders. Results obtained with CCK receptor antagonists in animal studies have been highly variable, and clinical trials with several of these compounds in anxiety disorders have been unsuccessful so far. However, future investigations using CCK receptor antagonists with better pharmacokinetic characteristics and animal models other than those validated with the classical anxiolytics benzodiazepines may permit a more precise evaluation of the potential of these compounds as anti-anxiety agents. Results obtained with peptide CRF receptor antagonists in animal models of anxiety convincingly demonstrated that the blockade of central CRF receptors may yield anxiolytic-like activity. However, the discovery of nonpeptide and more lipophilic CRF receptor antagonists is essential for the development of these agents as anxiolytics. Similarly, there is clear preclinical evidence that the central infusion of NPY and NPY fragments selective for the Y_1 receptor display anxiolytic-like effects in a variety of tests. However, synthetic nonpeptide NPY receptor agonists are still lacking, thereby hampering the development of NPY anxiolytics. Unlike selective NK_1 receptor antagonists, which have variable effects in anxiety models, peripheral administration of selective NK_2 receptor antagonists and central infusion of natriuretic peptides produce clear anxiolytic-like activity. Taken as a whole, these findings suggest that compounds targeting specific neuropeptide receptors may become an alternative to benzodiazepines for the treatment of anxiety disorders. PHARMACOL. THER. 82(1):1–61, 1999.

KEY WORDS. Anxiety disorders, cholecystokinin, corticotropin-releasing factor, natriuretic peptides, neuropeptide Y, tachykinins.

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ABBREVIATIONS. ACTH, adrenocorticotropic hormone; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; BZ, benzodiazepine; CCK, cholecystokinin; CNP, C-type natriuretic peptide; CRF, corticotropin-releasing factor; CSF, cerebrospinal fluid; GABA, γ-aminobutyric acid; GAD, generalized anxiety disorder; 5-HT, 5-hydroxytryptamine, serotonin; NE, norepinephrine; NK, neurokinin; NP, natriuretic peptide; NPY, neuropeptide Y; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin; OCD, obsessive-compulsive disorder; PP, pancreatic polypeptide; PYY, peptide YY; PVN, paraventricular nucleus; SP, substance P; TK, tachykinin.

1. INTRODUCTION

Since their introduction in the 1960s, benzodiazepines (BZs) have been the most commonly prescribed drugs for the treatment of anxiety (Lader, 1995). BZs produce their pharmacological effects by allosterically and positively modulating the fast inhibitory neurotransmission by γ-aminobutyric acid (GABA) at $GABA_A$ receptors (Squires *et al.*, 1979; Sieghart and Schuster, 1984). Although BZs remain the mainstay of drug treatment in anxiety disorders, research in this area has examined the involvement of other neurotransmitter systems over the past two decades. Much attention has focused on serotonin (5-hydroxytryptamine, 5-HT) neurotransmission and on the investigation of drugs that selectively interact with the 5-HT receptors (Griebel, 1995). However, after extensive research, only a few direct 5-HT-acting compounds have been launched as anxiolytic agents (e.g., buspirone and tandospirone) (Barradell and Fitton, 1996; Fulton and Brogden, 1997). In addition, only 5-HT reuptake inhibitors have been used successfully in the chronic treatment of panic attacks (Westenberg, 1996) and obsessive-compulsive disorders (OCDs) (Billett *et al.*, 1997). As a result, studies involving 5-HT drugs and anxiety behaviors have decreased within the past few years (Griebel, 1997). Nevertheless, the treatment of anxiety disorders remains an active area of research, and anxiolytic drug discovery focuses more and more on the involvement of neuroactive peptides in the modulation of anxiety behaviors. The rapid advances in understanding of gene structure and regulation of gene expression, the determination of peptide sequences, the characterization of their receptors, and the successful synthesis of both peptide and nonpeptide receptor ligands has increased the attraction for neuropeptides (Betancur *et al.*, 1997). As illustrated in Fig. 1, preclinical research with neuropeptides and anxiety has focused mainly on the behavioral effects of cholecystokinin (CCK) and corticotropin-releasing factor (CRF), but the involvement of other neuroactive peptides, such as neuropeptide Y (NPY), tachykinins (TKs) (substance P [SP] and neurokinin [NK] A and B), and natriuretic peptides (NPs), has also been examined.

This article reviews the literature on the role of CCK, CRF, NPY, TKs, and NPs in anxiety and stress-related behaviors. The focus is on a review of the results obtained with neuropeptide receptor ligands in experimental models of anxiety, but clinical findings are also considered.

2. EFFECTS OF NEUROPEPTIDE RECEPTOR LIGANDS ON ANXIETY-RELATED BEHAVIORS

2.1. *Cholecystokinin*

CCK is a peptide neurotransmitter that was originally found in the gut (Ivy and Oldberg, 1928), but which is extensively and abundantly distributed within the CNS (Van der Haegen *et al.*, 1975). It initially was identified as a 33 amino acid peptide (Mutt and Jorpes, 1971), but subsequent studies revealed the existence of multiple biologically active forms of CCK, including CCK_{58}, CCK_{39}, CCK_{33}, CCK_{22}, CCK_{8s} (sulfated), CCK_{8us} (unsulfated), CCK_7, CCK_5, and CCK_4 (Eysselein *et al.*, 1986). At present, CCK is recognized as the most widely distributed neuropeptide in the brain and the most promiscuous of the co-existing peptides, living with dopamine, vasoactive intestinal peptide, NPY, GABA, SP, and 5-HT (Fuxe *et al.*, 1980; Somogyi *et al.*, 1984; Hokfelt *et al.*, 1985; Boden *et al.*, 1991; Van Megen *et al.*, 1996). High levels of CCK-like immunoreactivity are present in the cerebral cortex, olfactory bulb, hypothalamus, amygdala, hippocampus, striatum, and spinal cord (Emson *et al.*, 1982). The predominant forms of CCK in the CNS are the CCK octapeptide (CCK_{8s}), whose sole tyrosine is sulfated, and the CCK tetrapeptide (CCK_4), although this latter exists in smaller concentrations (Dockray, 1976; Beinfeld and Palkovits, 1981). Two forms of CCK receptors have been characterized pharmacologically for their responsivity to the sulfated (CCK_A) or unsulfated (CCK_B) forms of CCK (Moran *et al.*, 1986). While CCK_A receptors are expressed in the alimentary tract and discrete regions of the brain (e.g., area postrema, posterior hypo-

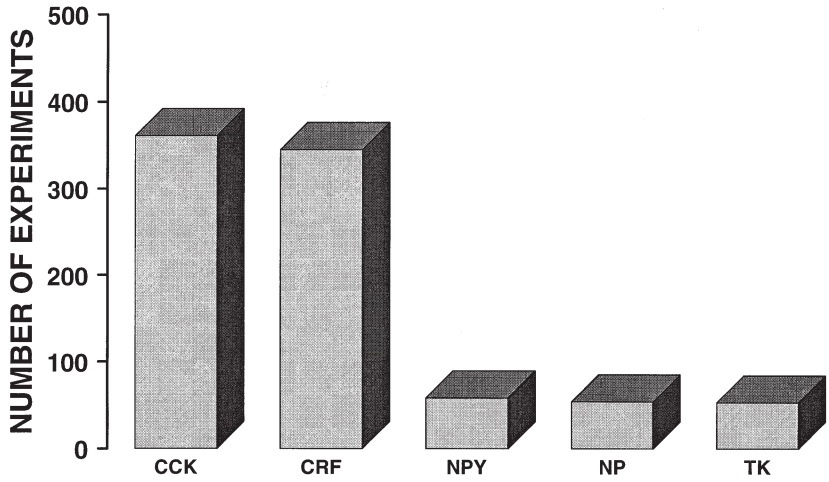

FIGURE 1. Analysis of the most extensively studied neuropeptides in anxiety models. The literature search covered the period up to March 1998.

thalamus, nucleus accumbens), CCK_B receptors are widely distributed in the CNS, with high levels found in the cortex, olfactory bulb, nucleus accumbens, amygdala, hippocampus, cerebellum, and hypothalamus (Pisegna *et al.*, 1992; de Weerth *et al.*, 1993). The neuroanatomical distribution of CCK has prompted speculation about its functional role in anxiety disorders, and has fueled both basic research and commercial interest in the CCK system, leading to numerous studies that investigated the behavioral action of CCK fragments and CCK receptor ligands in animal models of anxiety.

2.1.1. Behavioral effects of cholecystokinin fragments in animal models of anxiety. The first report of a possible involvement of CCK in the etiology of anxiety was published nearly 20 years ago by Della-Fera and Baile (1979), who observed that the synthetic peptide and CCK_B receptor agonist pentagastrin infused into the lateral ventricles of sheep produced behavioral modifications (foot stamping and vocalization) interpreted as increased fear. Subsequent experiments with pentagastrin and fractions of CCK confirmed the anxiogenic-like effects of these compounds (Table 1). However, as is made clear by Fig. 2, results have been highly variable and sometimes contradictory. For example, anxiogenic-like properties of CCK_{8s} and CCK_4 have been reported in 53% and 48% of the experiments, respectively, with opposite (i.e., anxiolytic) and/or no effects in the remainder. Although negative findings have been obtained in a variety of anxiety models, including rodent conflict tests and exploration procedures, it is noteworthy that anxiogenic-like effects have been reported, in the great part, in models based on exploratory activity, suggesting that these tests are more suitable for the investigation of CCK fragments than tests based on punished responses. Moreover, it has been suggested that the behavioral profile observed after CCK challenge depends on baseline anxiety levels (for reviews, see Harro *et al.*, 1993; Daugé and Roques, 1995). For example, in African green monkeys, CCK_4 produced behavioral changes indicative of fear (i.e., frozen immobility, crouching, cowering), mainly in subordinate animals that were often excessively reactive to the environment (Palmour *et al.*, 1992). Furthermore, after local injection of CCK_{8s} in the posterior part of the nucleus accumbens, anxiogenic-like effects were observed in the elevated plus-maze only when rats had not been habituated to the experimental room (Daugé *et al.*, 1989a,b). Consistent with this idea is the finding that caerulein, a peptide isolated from frog skin that shares the characteristic CCK amino acid sequence, decreased exploratory activity in the elevated plus-maze only when animals had not been isolated, gently handled by the experimenter, or habituated to the experimental environment (Vasar *et al.*, 1997).

The heterogeneity of response produced by CCK administration can also be explained by the fact that in some studies, CCK fragments have been infused in different brain areas in order to delineate the anatomical substrate of CCK-inducing anxiogenic-like effects. As an illustration, the local application of CCK_4 in the basolateral amygdala produced an increase in the startle response after acoustic stimulation, while perfusion in the dorsal periaqueductal gray matter, hippocampus, prefrontal cortex, or nucleus accumbens did not modify basal startle amplitude (Vaccarino *et al.*, 1997). However, studies with CCK_{8s} yielded a somewhat different profile. Thus, local application of CCK_{8s} produced anxiogenic-like effects in the elevated plus-maze when perfusion was performed in the amygdala (Belcheva *et al.*, 1994), posterior nucleus accumbens (Daugé *et al.*, 1989b, 1990), and dorsal periaqueductal gray matter (Guimaraes *et al.*, 1992), but not in the anterior nucleus accumbens (Daugé *et al.*, 1989a, 1990). Although the reasons for these differences are not clear yet, it is possible that the different affinities of CCK_{8s} and CCK_4 for the two CCK binding sites may account for this discrepancy. While CCK_A receptors display the highest affinity for the sulfated octapeptide and have 100-fold lower affinity for CCK_4, CCK_B receptors show the same affinity for both CCK fractions (Innis and Snyder, 1980).

Because CCK is co-localized with several neurotransmitters, a few studies have examined their role in the anxiogenic action of CCK. Using the elevated plus-maze test,

TABLE 1. Effects of Drugs Modulating CCK System in Animal Models of Anxiety

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
3*S*-(−)L-365,260	$CCK_{A/B}$ antagonist	Elevated plus-maze	CD-1 mice	0.1–10	i.p., 30	o		Rataud *et al.*, 1991
α-Methyltryptophan derivative	CCK_B antagonist	Light/dark test	Mice	0.0001–30	s.c., 40	+		Horwell *et al.*, 1991
			Mice	0.0001–10	p.o., 40	+		Horwell *et al.*, 1991
BC 197	CCK_B agonist	Elevated plus-maze	Wistar rats (200–220 g)	0.3	i.p., 30	—		Derrien *et al.*, 1994
		Light/dark test	Mice	0.001–3	i.p., 30	—		Daugé and Roques, 1995
BC 197 + CI-988		Elevated plus/maze	Wistar rats (200–220 g)	0.3	i.p., 30	(+)		Derrien *et al.*, 1994
BC 197 + CI-988 (0.1 mg/kg)		Light/dark test	Mice	0.01	i.p., 30	(+)		Daugé and Roques, 1995
BC 264	CCK_B agonist	Elevated plus/maze	Wistar rats (200–220 g)	0.003–300 pmol/0.2 μL	Posterior nucleus accumbens, 15	o		Daugé *et al.*, 1990
			Wistar rats (200–220 g)	0.03–300 pmol/0.2 μL	Anterior nucleus accumbens, 15	o		Daugé *et al.*, 1990
			Wistar rats (200–220 g)	0.03–10	i.p., 30	o		Derrien *et al.*, 1994
			Vagotomized Wistar rats (250 g)	0.3–300 μg/kg	i.p., 30	o		Ladurelle *et al.*, 1997
		Four-hole box	Wistar rats (200–220 g)	0.003–300 pmol/0.2 μL	Posterior nucleus accumbens, 15	o		Daugé *et al.*, 1990
			Wistar rats (200–220 g)	0.03–300 pmol/0.2 μL	Anterior nucleus accumbens, 15	o		Daugé *et al.*, 1990
		Safety signal withdrawal conflict procedure	Wistar rats (300–400 g)	0.004–1	i.p., 30	o		Charrier *et al.*, 1995
BC 264 + CI-988		Elevated plus-maze	Wistar rats (200–220 g)	0.3	i.p., 30	+	Co-administration produced anxiolytic-like effects	Derrien *et al.*, 1994
BC 264 + L-365,260		Elevated plus-maze	Wistar rats (200–220 g)	0.3	i.p., 30	—	No antagonism of the anxiogenic-like effects	Derrien *et al.*, 1994
BDNL	$CCK_{A/B}$ agonist	Elevated plus-maze	Wistar rats (200–220 g)	0.3–3	i.p., 30	—		Derrien *et al.*, 1994
BDNL + CI-988		Elevated plus-maze	Wistar rats (200–220 g)	0.3	i.p., 30	(+)		Derrien *et al.*, 1994
BDNL + devazepide		Elevated plus-maze	Wistar rats (200–220 g)	0.3	i.p., 30	(+)		Derrien *et al.*, 1994
BDNL + L-365,260		Elevated plus-maze	Wistar rats (200–220 g)	0.3	i.p., 30	—	No antagonism of the anxiogenic-like effects	Derrien *et al.*, 1994
Benzotript	CCK_A antagonist	Exploratory behaviors	Swiss-Webster mice (20–25 g)	0.1–100	i.p., 5	o	Mice were confronted with a novel fringed cardboard object	Crawley *et al.*, 1986
Benzotript + CCK_{8s} (5 μg)		Exploratory behaviors	Swiss-Webster mice (20–25 g)	0.1–100	i.p., 5	(+)	Mice were confronted with a novel fringed cardboard object	Crawley *et al.*, 1986
BOC-CCK_4	CCK_B agonist	Conflict test	Wistar and Lister rats (225–325 g)	0.01–0.05	i.p., 30	—		Rex *et al.*, 1994a
		DPAG stimulation	Wistar rats (300 g)	0.1–10	i.p., 30	o		Jenck *et al.*, 1996
		Elevated plus-maze	Vagotomized Wistar rats (250 g)	300 μg/kg	i.p., 30	—		Ladurelle *et al.*, 1997
			Wistar and Lister rats (225–325 g)	0.01	i.p., 30	—		Rex *et al.*, 1994a
			Female coloured-BFA guinea-pigs (395–445 g)	0.01	i.p., 40	—		Rex *et al.*, 1994b

			Rats	5 μg		—	Animals were brought to the experimental room just before testing	Vasar, 1997
			Rats	5 μg		o	Animals were handled, habituated, and nonisolated	Vasar, 1997
			Wistar rats (250–300 g)	20 ng/0.5 μL	Amygdala, 0	o		Huston *et al.*, 1998
		Flight induced by DLH injection into the DPAG	Lister hooded rats (180–265 g)	0.15	i.p., 0	—		Mongeau and Marsden, 1997
		Light/dark test	Wistar and Lister rats (225–325 g)	0.002 and 0.05	i.p., 30	—		Rex *et al.*, 1994a
		Ultrasonic vocalization test	Wistar and Lister rats (225–325 g)	0.01	i.p., 30	—		Rex *et al.*, 1994a
BOC-CCK_4 + naloxone (0.5 mg/kg)		Elevated plus-maze	Rats	1 μg		—		Vasar, 1997
Caerulein	$CCK_{A/B}$ agonist	Elevated plus-maze	Wistar rats	0.05	s.c., 15	—		Gacsalyi *et al.*, 1997
			Albino mice (22–25 g)	100 ng–10 μg	i.p., 15	—		Guimaraes *et al.*, 1992
			Male and female Wistar rats (220–280 g)	5 μg	s.c., 15	—		Männistö *et al.*, 1994
			Hooded Lister rats (200–250 g)	1–10 nmol/5 μL	i.c.v., 15	—		Singh *et al.*, 1991c
			Mice			—		Vasar *et al.*, 1994b
			Rats	5 μg		—	Animals were brought to the experimental room just before testing	Vasar, 1997
			Albino mice (22–25 g)	500 ng	i.p., 15	o	Animals were handled daily during 10 days	Guimaraes *et al.*, 1992
			Rats	5 μg		o	Animals were handled, habituated, and nonisolated	Vasar, 1997
Caerulein + buspirone (0.12–2.37 μmol/kg)		Elevated plus-maze	Wistar rats	0.05	s.c., 15	—	No antagonism of the anxiogenic effects of caerulein	Gacsalyi *et al.*, 1997
Caerulein + diazepam		Elevated plus-maze	Albino mice (22–25 g)	500 ng	i.p., 15	—	No antagonism of the anxiogenic-like effects	Guimaraes *et al.*, 1992
Caerulein + L-365,260		Elevated plus-maze	Rats	5 μg		(+)		Vasar, 1997
Caerulein + naloxone (0.5 mg/kg)		Elevated plus-maze	Rats	1 μg		—		Vasar, 1997
Caerulein + proglumide		Elevated plus-maze	Albino mice (22–25 g)	500 ng	i.p., 15	(+)		Guimaraes *et al.*, 1992
Caerulein + ritanserin (0.1–2.1 μmol/kg)		Elevated plus-maze	Wistar rats	0.05	s.c., 15	(+)		Gacsalyi *et al.*, 1997
Caerulein + vagotomy		Elevated plus-maze	Mice			—	Potentiation of the anxiogenic effects of caerulein	Vasar *et al.*, 1994b
CCK_4	CCK_B agonist	Acoustic startle reflex	Wistar rats	0.25–25 nM/ 0.5 μL	Basolateral amygdala, 0	—	200 Startle stimuli (500 msec; 83, 85, 90, 100, and 120 dB; VI, 15 sec) were presented	Vaccarino *et al.*, 1997
			Wistar rats	2.5–250 nM/ 5 μL	i.c.v., 0	—	200 Startle stimuli (500 msec; 83, 85, 90, 100, and 120 dB; VI, 15 sec) were presented	Vaccarino *et al.*, 1997

(*continued*)

TABLE 1. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
			Wistar rats	0.25–25 nM/ 0.5 μL	Periaqueductal gray, 0	o	200 Startle stimuli (500 msec; 83, 85, 90, 100, and 120 dB; VI, 15 sec) were presented	Vaccarino *et al.*, 1997
			Wistar rats	0.25–25 nM/ 0.5 μL	Hippocampus, 0	o	200 Startle stimuli (500 msec; 83, 85, 90, 100, and 120 dB; VI, 15 sec) were presented	Vaccarino *et al.*, 1997
			Wistar rats	0.25–25 nM/ 0.5 μL	Prefrontal cortex, 0	o	200 Startle stimuli (500 msec; 83, 85, 90, 100, and 120 dB; VI, 15 sec) were presented	Vaccarino *et al.*, 1997
			Wistar rats	0.25–25 nM/ 0.5 μL	Nucleus accumbens, 0	o	200 Startle stimuli (500 msec; 83, 85, 90, 100, and 120 dB; VI, 15 sec) were presented	Vaccarino *et al.*, 1997
		Conflict test	Rats	2–100 μg		—		Fink *et al.*, 1994
		DPAG stimulation	Wistar rats (300 g)	0.03–0.32	i.v., 5	o		Jenck *et al.*, 1996
			Wistar rats (300 g)	0.01–3.2	i.p., 30	o		Jenck *et al.*, 1996
		Elevated plus-maze	Female guinea-pigs BFA-outbred (395–445 g)	0.01	i.p., 40	—		Rex *et al.*, 1997
			Guinea-pigs	2–100 μg		—		Fink *et al.*, 1994
			DBA/2 mice (12–15 weeks)	12.5–100 μg	i.p., 30	o		Johnson and Rodgers, 1996
		Exploration box	Female Wistar rats (200–250 g)	0.075	s.c., 15	—		Matto *et al.*, 1997a
		Exploratory behaviors	Swiss-Webster mice (20–25 g)	10–200	i.p., 5	o	Mice were confronted with a novel fringed cardboard object	Crawley *et al.*, 1986
		Exposure to a clean cloth	Ovariectomized female Wistar rats (2 monts)	5–10 μg	i.p., 10	—	Unlike control rats, animals treated with the drug did not sniff nor pull the cloth, but they displayed freezing	Pavlasevic *et al.*, 1993
		Flight induced by DLH injection into the DPAG	Lister hooded rats (180–265 g)	0.002 μg/l μL	Periaqueductal gray, 0	o		Mongeau and Marsden, 1997
			Lister hooded rats (180–265 g)	0.4–40 μg/ 20 μL	i.c.v., 0	o		Mongeau and Marsden, 1997
		Free observation	African green monkeys	5–10 μg	i.v., 0	—	The drug engendered frozen immobility	Palmour *et al.*, 1991
			African green monkeys	0.5–4 μg	i.v., 0	—	Animals displayed behaviors indicative of fear	Palmour *et al.*, 1992
		Light/dark test	Mice	2–100 μg		—		Fink *et al.*, 1994
		Marble burying test	Sprague-Dawley rats (160–200 g)	1.2–4 nmol	s.c.	—		Csonka *et al.*, 1988
		Safety signal withdrawal conflict procedure	Wistar rats (300–400 g)	0.01–1	s.c., 30	o		Charrier *et al.*, 1995
		Social interaction test	Rats	2–100 μg		o		Fink *et al.*, 1994
		Tawney owl call-induced defensive behaviors	Mice			—		Hendrie and Weiss, 1994

		Ultrasonic vocalization test	Rats	2–100 μg		—		Fink *et al.*, 1994
CCK_4 + 8-OH-DPAT (0.3 mg/kg)		Elevated plus-maze	Female guinea-pigs BFA-outbred (395–445 g)	0.01	i.p., 40	(+)		Rex *et al.*, 1997
CCK_4 + CCK_8 (5 μg)		Exploratory behaviors	Swiss-Webster mice (20–25 g)	200	i.p., 5	(+)	Mice were confronted with a novel fringed cardboard object	Crawley *et al.*, 1986
CCK_4 + chlordiazepoxide (1.5 μmol/kg)		Marble burying test	Sprague-Dawley rats (160–200 g)	1.2–4 nmol	s.c.	(–)	CCK-4 blocked the inhibitory effect of chlordiazepoxide	Csonka *et al.*, 1988
CCK_4 + citalopram (10 mg/kg)		Exploration box	Female Wistar rats (200–250 g)	0.075	s.c., 15	—	No antagonism of the anxiogenic effects of CCK_4	Matto *et al.*, 1997a
CCK_4 + desipramine (10 mg/kg)		Exploration box	Female Wistar rats (200–250 g)	0.075	s.c., 15	—	No antagonism of the anxiogenic effects of CCK_4	Matto *et al.*, 1997a
CCK_4 + devazepide (1 mg/kg)		Exploration box	Female Wistar rats (200–250 g)	0.075	s.c., 15	—	No antagonism of the anxiogenic effects of CCK_4	Matto *et al.*, 1997a
CCK_4 + L-365,260 (1 mg/kg)		Exploration box	Female Wistar rats (200–250 g)	0.075	s.c., 15	(+)		Matto *et al.*, 1997a
CCK_4 + LY262691		Free observation	African green monkeys	5–30 μg	i.v., 0	(+)		Palmour *et al.*, 1991
CCK_{8s}	$CCK_{A/B}$ agonist	Acoustic startle reflex	Wistar rats	5 ng/0.5 μL	Caudal pontine reticular nucleus, 0	—	Rats received 40 startle stimuli (10 kHz, 100 dB SPL, 20 msec) just prior to and after drug administration	Fendt *et al.*, 1995
		Conflict test	Rats	2–100 μg		o		Fink *et al.*, 1994
			Wistar and Lister rats (225–325 g)	0.0002–0.025	i.p., 30	o		Rex *et al.*, 1994a
		Elevated plus-maze	Wistar rats (200–240 g)	0.01–1 μg/l μL	Right amygdala, 30	—		Belcheva *et al.*, 1994
			Wistar rats (200–240 g)	0.01–1 μg/l μL	Left amygdala, 30	—		Belcheva *et al.*, 1994
			Wistar rats (200–240 g)	0.01–1 μg/l μL	Left and right amygdala, 30	—		Belcheva *et al.*, 1994
			Wistar rats (200–250 g)	1 μg/2 μL	i.c.v., 30	—		Bíró *et al.*, 1993
			Wistar (200–250 g)	0.001/2 μL	i.c.v., 30	—		Bíró *et al.*, 1997
			Wistar rats (200–220 g)	3 fmol/0.2 μL	Posterior nucleus accumbens, 15	—		Daugé *et al.*, 1989b
			Wistar rats (200–220 g)	0.003 pmol/ 0.2 μL	Posterior nucleus accumbens, 15	—		Daugé *et al.*, 1990
			Wistar rats (250–300 g)	500 ng/0.5 μL	DPAG, 5	—		Guimaraes *et al.*, 1992
			Outbred female mice (20–25 g)	0.0025–0.01	s.c., 15	—		Vasar *et al.*, 1994a
			Wistar rats (200–220 g)	1–1000 fmol/ 0.2 μL	Anterior nucleus accumbens, 15	o		Daugé *et al.*, 1989b
			Wistar rats (200–220 g)	0.03 pmol/ 0.2 μL	Anterior nucleus accumbens, 15	o		Daugé *et al.*, 1990
			Guinea-pigs	2–100 μg		o		Fink *et al.*, 1994
			DBA/2 mice (12–15 weeks)	12.5–100 μg	i.p., 30	o		Johnson and Rodgers, 1996
			Wistar and Lister rats (225–325 g)	0.02	i.p., 30	o		Rex *et al.*, 1994a
			Wistar rats (250–300 g)	1 ng/0.5 μL	Amygdala, 0	o		Huston *et al.*, 1998
		Elevated zero-maze	Sprague-Dawley rats (200–250 g)	0.01–0.1	i.p., 30	o		Chopin and Briley, 1993

(*continued*)

TABLE 1. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
		Exploratory behaviors	Swiss-Webster mice (20–25 g)	5 μg	i.p., 5	—	Mice were confronted with a novel fringed cardboard object	Crawley *et al.*, 1986
		Four-hole box	Sprague-Dawley rats (200–220 g)	1 fmol–100 pmol/1 μL	Median nucleus accumbens, 0	—		Daugé *et al.*, 1989a
			Wistar rats (200–220 g)	0.1–3 fmol/ 0.2 μL	Posterior nucleus accumbens, 15	—		Daugé *et al.*, 1989b
			Wistar rats (200–220 g)	0.003 pmol/ 0.2 μL	Posterior nucleus accumbens, 15	—		Daugé *et al.*, 1990
			Wistar rats (200–220 g)	1–1000 fmol/ 0.2 μL	Anterior nucleus accumbens, 15	o		Daugé *et al.*, 1989b
			Wistar rats (200–220 g)	0.03 pmol/ 0.2 μL	Anterior nucleus accumbens, 15	o		Daugé *et al.*, 1990
		Light/dark test	CD-1 mice (5 weeks)	25–50 ng/1 μL	i.c.v., 15	—		MacNeil *et al.*, 1997
			Wistar and Lister rats (225–325 g)	0.001–0.005	i.p., 30	+		Rex *et al.*, 1994a
			Mice	2–100 μg		o		Fink *et al.*, 1994
		Marble burying test	Sprague-Dawley rats (160–200 g)	1.2–4 nmol	s.c.	—		Csonka *et al.*, 1988
			Sprague-Dawley rats (160–200 g)	1.2–4 pmol	i.c.v.	—		Csonka *et al.*, 1988
		Open-field	Sprague-Dawley rats (200–220 g)	100 pmol/1 μL	Median nucleus accumbens, 0	—		Daugé *et al.*, 1989a
			Sprague-Dawley rats (200–220 g)	1 fmol–100 pmol/1 μL	Median nucleus accumbens, 0	o	Rats were habituated to the environment	Daugé *et al.*, 1989a
		Social interaction test	Rats	2–100 μg		o		Fink *et al.*, 1994
		Ultrasonic vocalization test	Rats	2–100 μg		o		Fink *et al.*, 1994
			Wistar and Lister rats (225–325 g)	0.005	i.p., 30	o		Rex *et al.*, 1994a
CCK_{8s} + α-helical $CRF_{9–41}$		Elevated plus-maze	Wistar rats (200–250 g)	0.001–1 μg/ 2 μL	i.c.v., 30	(+)		Bíró *et al.*, 1993
CCK_{8s} + atropine (2 mg/kg)		Elevated plus-maze	Wistar (200–250 g)	0.001/2 μL	i.c.v., 30	(+)		Bíró *et al.*, 1997
CCK_{8s} + bicuculline (5 mg/kg)		Elevated plus-maze	Wistar (200–250 g)	0.001/2 μL	i.c.v., 30	—	No antagonism of the anxiogenic effects of CCK_8	Bíró *et al.*, 1997
CCK_{8s} + chlordiazepoxide (1.5 μmol/kg)		Marble burying test	Sprague-Dawley rats (160–200 g)	1.2–4 nmol	s.c.	(–)	CCK_{8s} blocked the inhibitory effect of chlordiazepoxide	Csonka *et al.*, 1988
CCK_{8s} + chlordiazepoxide (1.5 μmol/kg)		Marble burying test	Sprague-Dawley rats (160–200 g)	12–40 fmol	Amygdala	(–)	CCK_{8s} blocked the inhibitory effect of chlordiazepoxide	Csonka *et al.*, 1988
		Marble burying test	Sprague-Dawley rats (160–200 g)	1.2–4 fmol	Nucleus accumbens	+	CCK_{8s} did not block the inhibitory effect of chlordizepoxide	Csonka *et al.*, 1988
CCK_{8s} + CRF antiserum		Elevated plus-maze	Wistar rats (200–250 g)		i.c.v., 30	(+)		Bíró *et al.*, 1993
CCK_{8s} + devazepide		Elevated plus-maze	Wistar rats (200–220 g)	3 fmol/0.2 μL	Posterior nucleus accumbens, 15	(+)		Daugé *et al.*, 1989b

		Four-hole box	Wistar rats (200–220 g)	0.1–3 fmol/ 0.2 μL	Posterior nucleus accumbens, 15	(+)		Daugé *et al.*, 1989b
CCK_{8s} + haloperidol (0.01 mg/kg)		Elevated plus-maze	Wistar (200–250 g)	0.001/2 μL	i.c.v., 30	(+)		Bíró *et al.*, 1997
CCK_{8s} + methysergide (5 mg/kg)		Elevated plus-maze	Wistar (200–250 g)	0.001/2 μL	i.c.v., 30	—	No antagonism of the anxiogenic effects of CCK_8	Bíró *et al.*, 1997
CCK_{8s} + naloxone (0.1 mg/kg)		Elevated plus-maze	Wistar (200–250 g)	0.001/2 μL	i.c.v., 30	(+)		Bíró *et al.*, 1997
CCK_{8s} + phenoxy-benzamine (2 mg/kg)		Elevated plus-maze	Wistar (200–250 g)	0.001/2 μL	i.c.v., 30	—	No antagonism of the anxiogenic effects of CCK_8	Bíró *et al.*, 1997
CCK_{8s} + propranolol (10 mg/kg)		Elevated plus-maze	Wistar (200–250 g)	0.001/2 μL	i.c.v., 30	—	No antagonism of the anxiogenic effects of CCK_8	Bíró *et al.*, 1997
CCK_{8us}	CCK_B agonist	Elevated plus-maze	Wistar rats (200–220 g)	0.1–1000 fmol/ 0.2 μL	Posterior nucleus accumbens, 15	o		Daugé *et al.*, 1989b
			Wistar rats (200–220 g)	10–10,000 fmol/ 0.2 μL	Anterior nucleus accumbens, 15	o		Daugé *et al.*, 1989b
		Elevated zero-maze	Sprague-Dawley rats (200–250 g)	0.001, 0.01–0.03	i.p., 30	—		Chopin and Briley, 1993
		Four-hole box	Wistar rats (200–220 g)	0.1–1000 fmol/ 0.2 μL	Posterior nucleus accumbens, 15	o		Daugé *et al.*, 1989b
			Wistar (200–220 g)	10–10,000 fmol/0.2 μL	Anterior nucleus accumbens, 15	o		Daugé *et al.*, 1989b
		Light/dark test	Swiss mice (25–30 g)	0.003–0.3	i.p., 30	—		Chopin and Briley, 1993
		Marble burying test	Sprague-Dawley rats (160–200 g)	1.2–4 nmol	s.c.	—		Csonka *et al.*, 1988
			Sprague-Dawley rats (160–200 g)	1.2–4 pmol	i.c.v.	—		Csonka *et al.*, 1988
CCK_{8us} + chlordiazepoxide (1.5 μmol/kg)		Marble burying test	Sprague-Dawley rats (160–200 g)	1.2–4 nmol	s.c.	(–)	CCK_{8us} blocked the inhibitory effect of chlordiazepoxide	Csonka *et al.*, 1988
		Marble burying test	Sprague-Dawley rats (160–200 g)	12–40 fmol	Amygdala	(–)	CCK_{8us} blocked the inhibitory effect of chlordiazepoxide	Csonka *et al.*, 1988
		Marble burying test	Sprague-Dawley rats (160–200 g)	1.2–4 fmol	Nucleus accumebens	+	CCK_{8us} did not block the inhibitory effect of chlordiazepoxide	Csonka *et al.*, 1988
CCK_{8us} + flumazenil (4 mg/kg)		Elevated zero-maze	Sprague-Dawley rats (200–250 g)	0.01	i.p., 30	(+)		Chopin and Briley, 1993
CI-988	CCK_B antagonist	Conditioned emotional response	Rats	0.01–10		o		Daugé *et al.*, 1990
			Rats	0.001–10	s.c., 30	o		Dourish *et al.*, 1994
		Conditioned suppression of drinking	Rats	0.01–10		o		Daugé *et al.*, 1990
		Conflict procedure	Squirrel monkeys	0.1–10		o		Daugé *et al.*, 1990
		Conflict test	Squirrel monkeys (600–800 g)	0.03–3	i.m., 0	+	An FI3-min schedule was used	Powell and Barrett, 1991
		DPAG stimulation	Wistar rats (300 g)	3.2–32	i.p., 30	o		Jenck *et al.*, 1996
		Elevated plus-maze	Rats	0.01–1	s.c., 45	+		Costall *et al.*, 1991
			Hooded Lister rats (250–300 g)	0.1–10	i.p., 40	+		Field *et al.*, 1991

(*continued*)

TABLE 1. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
			Hooded Lister rats (250–300 g)	1	i.p., 40	+		Hinks *et al.*, 1996
			Hooded Lister rats (275–325 g)	0.01–1	s.c., 40	+		Hughes *et al.*, 1990
			Hooded Lister rats (200–250 g)	0.01–10	p.o., 40	+		Singh *et al.*, 1991a
			Hooded Lister rats (200–250 g)	0.1–10 μmol	i.p., 40	+		Singh *et al.*, 1991c
			Rats	0.01–1		o		Daugé *et al.*, 1990
			Wistar rats (200–220 g)	0.002–0.2	i.p., 45	o		Derrien *et al.*, 1994
		Elevated zero-maze	Hooded Lister rats (250–320 g)	0.2	s.c., 30	+		Bickerdike *et al.*, 1994
			Rats	0.001–10	s.c., 30	o		Dourish *et al.*, 1994
		Geller-Seifter conflict test	Hooded Lister rats (200–250 g)	0.01	i.p., 40	+	A VI30/FR5 schedule was used	Singh *et al.*, 1991a
		Human threat	Marmoset	0.01–1	s.c., 45	+		Costall *et al.*, 1991
			Marmoset (290–390 g)	1	s.c., 40	+		Hughes *et al.*, 1990
		Light/dark test	BKW mice (30–35 g)	0.001–0.1	i.p., 40	+		Costall and Naylor, 1997
			Mice	0.0001–30	s.c., 40	+		Costall *et al.*, 1991
			Mice	0.01	s.c., 2–12 hr	+		Costall *et al.*, 1991
			TO mice (25–30 g)	0.1–10	i.p., 40	+		Field *et al.*, 1991
			Albino mice (Bradford strain, 20–30 g)	0.0001–30	p.o., 40	+		Hughes *et al.*, 1990
			Albino mice (Bradford strain, 20–30 g)	0.0001–10	s.c., 40	+		Hughes *et al.*, 1990
			Albino mice (Bradford strain, 20–30 g)		During 7 days (×2)	+		Hughes *et al.*, 1990
			TO mice (20–25 g)	0.1–1	i.p., 40	+		Singh *et al.*, 1991a
			TO mice (20–25 g)	0.01–10	p.o., 40	+		Singh *et al.*, 1991a
			TO mice (20–25 g)	1	i.p., during 7 days (×2)	+	Effects were observed 8 hr after the last injection	Singh *et al.*, 1992
		Safety signal withdrawal conflict procedure	Wistar rats (300–400 g)	0.01–1	s.c., 30	o		Charrier *et al.*, 1995
		Social interaction test	Hooded Lister rats (250–300 g)	0.01–1	i.p., 40	+		Field *et al.*, 1991
			Rats	0.001–1	s.c., 45	+	High light unfamiliar condition	Costall *et al.*, 1991
			Hooded Lister rats (275–325 g)	0.001–1	s.c., 40	+		Hughes *et al.*, 1990
			Hooded Lister rats (200–250 g)	0.01–3	i.p., 40	+		Singh *et al.*, 1991a
CI-988 + alcohol withdrawal		Light/dark test	Mice	1	i.p.	(+)	Antagonism of the anxiogenic effects of alcohol withdrawal	Costall *et al.*, 1991
CI-988 + cocaine withdrawal		Light/dark test	Mice	1	i.p.	(+)	Antagonism of the anxiogenic effects of cocaine withdrawal	Costall *et al.*, 1991
CI-988 + diazepam withdrawal		Light/dark test	Mice	1	i.p.	(+)	Antagonism of the anxiogenic effects of diazepam withdrawal	Costall *et al.*, 1991

		Light/dark test	Albino mice (Bradford strain, 20–30 g)			(+)	Antagonism of the anxiogenic-like effects of diazepam withdrawal	Hughes *et al.*, 1990
		Light/dark test	TO mice (20–25 g)	1	i.p., during 7 days (×2)	(+)		Singh *et al.*, 1992
CI-988 + nicotine withdrawal		Light/dark test	Mice	1	i.p.	(+)	Antagonism of the anxiogenic effects of nicotine withdrawal	Costall *et al.*, 1991
CI-988 + pentagastrin		Elevated plus-maze	Hooded Lister rats (200–250 g)	0.5–5 μmol	i.p., 15	(+)		Singh *et al.*, 1991c
CI-988 + PTZ		Elevated plus-maze	Hooded Lister rats (200–250 g)	0.5–5 μmol	i.p., 15	—	No antagonism of the anxiogenic-like effects of PTZ	Singh *et al.*, 1991c
CI-988 + ritanserin (1 mg/kg)		Light/dark test	BKW mice (30–35 g)	0.001–0.1	i.p., 40	+	No interaction	Costall and Naylor, 1997
CI-988 + zimelidine (3–6 mg/kg)		Elevated zero-maze	Hooded Lister rats (250–320 g)	0.1–0.2	s.c., 30	o	No interaction	Bickerdike *et al.*, 1994
Compound **10**	CCK_B antagonist	Elevated plus-maze	Mice	0.001–1	i.p., 30	o	The drug is an amino acid-derived piperidide	Holladay *et al.*, 1995
Compound **24**	CCK_B antagonist	Elevated plus-maze	Mice	0.1	i.p., 30	+	The drug is an amino acid-derived piperidide	Holladay *et al.*, 1995
Compound **36**	CCK_B antagonist	Elevated plus-maze	Mice	0.001	i.p., 30	+	The drug is an amino acid-derived piperidide	Holladay *et al.*, 1995
Devazepide	CCK_A antagonist	Conditioned emotional response	Rats	0.001–10	s.c., 30	o		Dourish *et al.*, 1994
		Elevated plus-maze	Hooded Lister rats (7 days)	0.015	s.c., 30	+	Rats were reared from weaning (21 days) in social groups (5/cage)	Bickerdike and Marsden, 1994
			Sprague-Dawley rats (250–300 g)	1–10 μg	s.c., 30	+		Ravard *et al.*, 1990
			Hooded Lister rats (7 days)	0.015	s.c., 30	o	Rats were reared from weaning (21 days) individually	Bickerdike and Marsden, 1994
			Wistar rats (200–220 g)	0.1–0.2	i.p., 45	o		Daugé *et al.*, 1989b
			Wistar rats (200–220 g)	0.002–0.2	i.p., 45	o		Derrien *et al.*, 1994
		Elevated plus-maze	DBA/2 mice (12–15 weeks)	0.001–1	i.p., 30	o		Johnson and Rodgers, 1996
			Male and female Wistar rats (220–280 g)	1–100 μg	i.p., 30	o		Männistö *et al.*, 1994
			CD-1 mice	0.1–10	i.p., 30	o		Rataud *et al.*, 1991
			Outbred female mice (20–25 g)	0.0001–0.1	i.p., 30	o		Vasar *et al.*, 1994a
		Elevated zero-maze	Hooded Lister rats (7 days)	0.015	s.c., 30	+	Rats were reared from weaning (21 days) in social groups (5/cage)	Bickerdike and Marsden, 1994
			Hooded Lister rats (250–320 g)	0.015	s.c., 30	+		Bickerdike *et al.*, 1994
			Sprague-Dawley rats (200–250 g)	0.01–0.3	i.p., 30	+		Chopin and Briley, 1993
			Rats	0.001–10	s.c., 30	+		Dourish *et al.*, 1994
			Hooded Lister rats (7 days)	0.015	s.c., 30	o	Rats were reared from weaning (21 days) individually	Bickerdike and Marsden, 1994
			Female Wistar rats (200–250 g)	0.01–1	i.p., 30	o		Matto *et al.*, 1997b
		Exploration box	Female Wistar rats (200–250 g)	1	i.p., 30	o		Matto *et al.*, 1997a

(*continued*)

TABLE 1. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
		Four-hole box	Wistar rats (200–220 g)	0.1–0.2	i.p., 45	o		Daugé *et al.*, 1989b
		Light/dark test	Swiss mice (20–25 g)	0.1	i.p., 30	+		Ballaz *et al.*, 1997
			Swiss mice (25–30 g)	0.001–0.3	i.p., 30	+		Chopin and Briley, 1993
			BKW mice (30–35 g)	0.1–1	i.p., 40	+		Costall and Naylor, 1997
			DBA/2 mice (20–25 g)	0.0005–0.005	i.p., 30	+		Hendrie and Dourish, 1990
			DBA/2 mice (20–30 g)	0.05–5000 μg	30	+		Hendrie *et al.*, 1993
			TO mice (20–25 g)	0.5–20	i.p., 40	o		Singh *et al.*, 1991a
		Safety signal withdrawal conflict procedure	Wistar rats (300–400 g)	0.001–1	s.c., 30	o		Charrier *et al.*, 1995
		Social interaction test	Hooded Lister rats (200–250 g)	5–40	i.p., 40	o		Singh *et al.*, 1991a
		Vogel conflict test	Wistar rats (190–210 g)	0.2	i.p., 30	+	Animals received an electric shock of 0.1 mA, 2 sec every 20 licks	Ballaz *et al.*, 1997
Devazepide + caerulein		Elevated plus-maze	Mice			—	Potentiation of the anxiogenic effects of caerulein	Vasar *et al.*, 1994b
Devazepide + caerulein (5 μg)		Elevated plus-maze	Male and female Wistar rats (220–280 g)	1–100 μg	i.p., 30	—	The anxiogenic-like effects were potentiated	Männistö *et al.*, 1994
Devazepide + CCK_8 (0.0025 mg/kg)		Elevated plus-maze	Outbred female mice (20–25 g)	0.0001–0.1	i.p., 30	—	Potentiation of the anti-exploratory effects of CCK_8. (probably nonspecific effects)	Vasar *et al.*, 1994a
Devazepide + citalopram (10 mg/kg)		Exploration box	Female Wistar rats (200–250 g)	1	i.p., 30	o	No interaction	Matto *et al.*, 1997a
Devazepide + desipramine (10 mg/kg)		Exploration box	Female Wistar rats (200–250 g)	1	i.p., 30	o	No interaction	Matto *et al.*, 1997a
Devazepide + flumazenil (4 mg/kg)		Elevated zero-maze	Sprague-Dawley rats (200–250 g)	0.01	i.p., 30	(–)		Chopin and Briley, 1993
Devazepide + ritanserin (1 mg/kg)		Light/dark test	BKW mice (30–35 g)	0.001–1	i.p., 40	+	Potentiation of the anxiolytic-like effects of devazepide	Costall and Naylor, 1997
Devazepide + Wy27587 (6 mg/kg, SSRI)		Elevated zero-maze	Rats	0.001–10	s.c., 30	(–)		Dourish *et al.*, 1994
Devazepide + Wy27587 (3–6 mg/kg)		Elevated zero-maze	Hooded Lister rats (250–320 g)	0.015	s.c., 30	(–)		Bickerdike *et al.*, 1994
Devazepide + zimelidine (3 mg/kg)		Elevated zero-maze	Rats	0.001–10	s.c., 30	(–)		Dourish *et al.*, 1994
Devazepide + zimelidine (3–6 mg/kg)		Elevated zero-maze	Hooded Lister rats (250–320 g)	0.015	s.c., 30	(–)		Bickerdike *et al.*, 1994
IQM-95,333	CCK_A antagonist	Light/dark test	Swiss mice (20–25 g)	0.01–5	i.p., 30	+		Ballaz *et al.*, 1997

		Vogel conflict test	Wistar rats (190–210 g)	0.5–1	i.p., 30	+	Animals received an electric shock of 0.1 mA, 2 sec every 20 licks	Ballaz *et al.*, 1997
L-365,031	CCK_A antagonist	Elevated plus-maze	Sprague-Dawley rats (250–300 g)	0.01–100 μg	s.c., 30	o		Ravard *et al.*, 1990
		Light/dark test	DBA/2 mice (20–30 g)	5 μg	30	+		Hendrie *et al.*, 1993
L-365,260	CCK_B antagonist	Acoustic startle reflex	Rats	2	i.p., 2 hr	+	Animals underwent amphetamine withdrawals	Bush *et al.*, 1997
		Acoustic startle reflex	Rats	2	i.p., 2 hr	o		Bush *et al.*, 1997
		Conditioned emotional response	Rats	0.0001–0.1		o		Daugé *et al.*, 1990
			Rats	0.001–10	s.c., 30	o		Dourish *et al.*, 1994
		Conditioned suppression of drinking	Rats	0.0001–0.1		o		Daugé *et al.*, 1990
		Conflict procedure	Squirrel monkeys	1–50		o		Daugé *et al.*, 1990
		DPAG stimulation	Wistar rats (300 g)	3.2–32	i.p., 30	+		Jenck *et al.*, 1996
		Elevated plus-maze	Rats	0.001	During 14 days (×2)	—		Vasar *et al.*, 1997
			CD-1 mice	0.01–1	i.p., 30	+		Rataud *et al.*, 1991
			Sprague-Dawley rats (250–300 g)	1–10 μg	s.c., 30	+		Ravard *et al.*, 1990
			Female coloured-BFA guinea-pigs (395–445 g)	0.1	i.p., 30	+		Rex *et al.*, 1994b
			Hooded Lister rats (200–250 g)	0.25–25 μmol	i.p., 40	+		Singh *et al.*, 1991c
			Rats	1–100 μg		+		Vasar, 1997
			Rats	0.00001–10		o		Daugé *et al.*, 1990
			Wistar rats (200–220 g)	0.002–0.02	i.p., 45	o		Derrien *et al.*, 1994
			DBA/2 mice (12–15 weeks)	0.001–1	i.p., 30	o		Johnson and Rodgers, 1996
			Male and female Wistar rats (220–280 g)	1–100 μg	i.p., 30	o		Männistö *et al.*, 1994
			Outbred female mice (20–25 g)	0.001–1	i.p., 30	o		Vasar *et al.*, 1994a
		Elevated zero-maze	Hooded Lister rats (250–320 g)	0.001–1	s.c., 30	+		Bickerdike *et al.*, 1994
			Sprague-Dawley (200–250 g)	0.001–0.03	i.p., 30	+		Chopin and Briley, 1993
			Female Wistar rats (200–250 g)	1–5	i.p., 30	+		Matto *et al.*, 1997b
			Rats	0.001–10	s.c., 30	o		Dourish *et al.*, 1994
		Exploration box	Female Wistar rats (200–250 g)	1	i.p., 30	o		Matto *et al.*, 1997a
		Exposure to a cloth on which a cat had been sleeping	Ovariectomized female Wistar rats (2 months)	50–200 μg	i.p., 10	+	The drug prevented freezing	Pavlasevic *et al.*, 1993
		Fear-potentiated startle reflex	Wistar rats (275–325 g)	1–10	i.p., 30	+		Josselyn *et al.*, 1995a

(*continued*)

TABLE 1. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
		Ligh/dark test	Swiss mice (20–25 g)	0.01–0.1	i.p., 30	+		Ballaz *et al.*, 1997
			Swiss mice (25–30 g)	0.001–0.1	i.p., 30	+		Chopin and Briley, 1993
			TO mice (20–25 g)	1	i.p., 40	+		Singh *et al.*, 1991a
			DBA/2 mice (20–30 g)	0.005–500 μg	30	o		Hendrie *et al.*, 1993
		Safety signal withdrawal conflict procedure	Wistar rats (300–400 g)	0.004–2	i.p., 30	o		Charrier *et al.*, 1995
		Social interaction test	Hooded Lister rats (200–250 g)	3	i.p., 40	+		Singh *et al.*, 1991a
		Vogel conflict test	Wistar rats (190–210 g)	0.1	i.p., 30	+	Animals received an electric shock of 0.1 mA, 2 sec every 20 licks	Ballaz *et al.*, 1997
L-365,260 + BOC-CCK_4 (0.01 mg/kg)		Elevated plus-maze	Female coloured-BFA guinea-pigs (395–445 g)	0.1	i.p., 30	(+)		Rex *et al.*, 1994b
L-365,260 + BOC-CCK_4 (0.01 mg/kg)		Ultrasonic vocalization test	Wistar and Lister rats (225–325 g)	0.1	i.p., 30	(+)		Rex *et al.*, 1994a
L-365,260 + caerulein		Elevated plus-maze	Mice			(+)		Vasar *et al.*, 1994b
L-365,260 + caerulein (0.05 mg/kg)		Elevated plus-maze	Wistar rats	0.05	s.c., 15	(+)		Gacsalyi *et al.*, 1997
L-365,260 + caerulein (5 μg)		Elevated plus-maze	Male and female Wistar rats (220–280 g)	10 μg	i.p., 30	(+)		Männistö *et al.*, 1994
L-365,260 + CCK_4		Elevated plus-maze	Guinea-pigs	100 μg		(+)		Fink *et al.*, 1994
		Tawny owl call-induced defensive behaviors	Mice			(+)		Hendrie and Weiss, 1994
L-365,260 + CCK_8 (0.0025 mg/kg)		Elevated plus-maze	Outbred female mice (20–25 g)	0.01–1	i.p., 30	—	Potentiation of the anti-exploratory effects of CCK_8 (probably nonspecific effects)	Vasar *et al.*, 1994a
L-365,260 + citalopram (10 mg/kg)		Exploration box	Female Wistar rats (200–250 g)	1	i.p., 30	o	No interaction	Matto *et al.*, 1997a
L-365,260 + desipramine (10 mg/kg)		Exploration box	Female Wistar rats (200–250 g)	1	i.p., 30	o	No interaction	Matto *et al.*, 1997a
L-365,260 + flumazenil (4 mg/kg)		Elevated zero-maze	Sprague-Dawley rats (200–250 g)	0.01	i.p., 30	(–)		Chopin and Briley, 1993
L-365,260 + pentagastrin (10 nM)		Acoustic startle reflex	Wistar rats (275–300 g)	0.1	i.p., 10	(+)	Rats received 60 startle stimuli (119 dB) prior to drug administration	Frankland *et al.*, 1997
L-740,093	CCK_B antagonist	Conditioned emotional response	Rats	0.1–1		o		Daugé *et al.*, 1990

		Conditioned suppression of drinking	Rats	0.1–1		o		Daugé *et al.*, 1990
		Elevated plus-maze	Rats	0.1–1		o		Daugé *et al.*, 1990
Lorglumide	CCK_A antagonist	Conditioned freezing	Sprague-Dawley rats (250–300 g)	1	s.c., 30	+		Izumi *et al.*, 1996
		Elevated plus-maze	Sprague-Dawley rats (180–230 g)	0.3–3	i.p., 30	o		Griebel *et al.*, 1997a
		Light/dark test	BALB/c mice (7 weeks old)	1–10	i.p., 30	o		Griebel *et al.*, 1997a
		Mouse defense test battery	Swiss mice (10 weeks old)	0.3–10	i.p., 30	o		Griebel *et al.*, 1997a
		Punished drinking test	Sprague-Dawley rats (180–230 g)	0.3–10	i.p., 30	o		Griebel *et al.*, 1997a
		Punished lever pressing test	Wistar rats (400–500 g)	0.3–3	i.p., 30	o		Griebel *et al.*, 1997a
		Safety signal withdrawal conflict procedure	Wistar rats (300–400 g)	0.01–1	s.c., 20	o		Charrier *et al.*, 1995
Loxiglumide	$CCK_{A/B}$ antagonist	Conditioned freezing	Sprague-Dawley rats (250–300 g)	3–30	s.c., 30	o		Izumi *et al.*, 1996
LY247348	CCK_B antagonist	Punished responding	Squirrel monkeys	0.3–10	p.o.	+	An FR30 schedule was used	Barrett *et al.*, 1991
LY262,684	CCK_B antagonist	Punished responding	Squirrel monkeys	0.3–10	p.o.	+	An FR30 schedule was used	Barrett *et al.*, 1991
LY262,691	CCK_B antagonist	Free observation	African green monkeys	12	s.c., 60	+	The drug reduced the frequency of restless behavior	Palmour *et al.*, 1991
		Punished responding	Squirrel monkeys	0.3–10	p.o.	+	An FR30 schedule was used	Barrett *et al.*, 1991
		Safety signal withdrawal conflict procedure	Wistar rats (300–400 g)	0.001–1	s.c., 30	o		Charrier *et al.*, 1995
LY288513	CCK_B antagonist	Acoustic startle reflex	Long-Evans rats (150–350 g)	30–100	i.p., 60	o		Rasmussen *et al.*, 1993
			Long-Evans rats (150–350 g)	10–60	i.p., 60	o		Rasmussen *et al.*, 1996
		Cat exposure + elevated plus-maze	Hooded rats (140 g)	30–60	i.p.	(+)	Animals were injected 30 min after cat exposure and tested 1 week later	Adamec *et al.*, 1997
		Conditioned freezing	Sprague-Dawley rats (250–300 g)	0.03–0.3	s.c., 30	+		Izumi *et al.*, 1996
		Elevated plus-maze	Sprague-Dawley rats (280–330 g)	10	i.p., 30	+		Helton *et al.*, 1996
			Sprague-Dawley rats (280–330 g)	10–30	p.o., 60	+		Helton *et al.*, 1996
			Sprague-Dawley rats (180–230 g)	0.3–10	i.p., 30	o		Griebel *et al.*, 1997a
		Exploration box	Male and female Wistar rats (230–260 g)	0.01	i.p., 30	+	Exploratory activity was increased on the third exposure to the test situation	Harro *et al.*, 1995
		Light/dark test	BALB/c mice (7 weeks old)	0.1–10	i.p., 30	o		Griebel *et al.*, 1997a

(*continued*)

TABLE 1. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
		Mouse defense test battery	Swiss mice (10 weeks old)	1–3	i.p., 30	+	Positive effects on flight behavior only	Griebel *et al.*, 1997a
		Punished drinking test	Sprague-Dawley rats (180–230 g)	0.3–10	i.p., 30	o		Griebel *et al.*, 1997a
		Punished lever pressing test	Wistar rats (400–500 g)	0.1–10	i.p., 30	o		Griebel *et al.*, 1997a
LY288513 + caerulein		Elevated plus-maze	Mice			(+)		Vasar *et al.*, 1994b
LY288513 + CCK_4		Tawny owl call-induced defensive behaviors	Mice			(+)		Hendrie and Weiss, 1994
LY288513 + diazepam withdrawal		Acoustic startle reflex	Long-Evans rats (150–350 g)	60–100	i.p., 60	(+)	Antagonism of the anxiogenic effects of diazepam withdrawal	Rasmussen *et al.*, 1993
LY288513 + DSP-4		Exploration box	Male and female Wistar rats (230–260 g)	0.01	i.p., 30	o	The drug did not increase the exploratory activity in DSP-4 treated animals	Harro *et al.*, 1995
MK-329	CCK_A antagonist	Cat exposure	Hooded rats (140 g)	0.1–1	i.p.	o		Adamec *et al.*, 1997
		Cat exposure + elevated plus-maze	Hooded rats (140 g)	0.1–1	i.p.	—	(1) No antagonism of the anxiogenic effects of cat exposure (2) Animals were injected 30 min before cat exposure and tested 1 week later	Adamec *et al.*, 1997
			Hooded rats (140 g)	0.1–1	i.p.	—	(1) No antagonism of the anxiogenic effects of cat exposure (2) Animals were injected 30 min before cat exposure and tested 1 week later	Adamec *et al.*, 1997
		Elevated plus-maze	Hooded Lister rats (200–250 g)	50 μmol	i.p., 40	+		Singh *et al.*, 1991c
PD135158	CCK_B antagonist	Cat exposure	Hooded rats (140 g)	1–2	i.p.	+	The drug increased active defense	Adamec *et al.*, 1997
		Cat exposure + elevated plus-maze	Hooded rats (140 g)	1–2	i.p.	+	(1) No antagonism of the anxiogenic effects of cat exposure (2) Animals were injected 30 min before cat exposure and tested 1 week later	Adamec *et al.*, 1997
			Hooded rats (140 g)	1–2	i.p.	+	(1) No antagonism of the anxiogenic effects of cat exposure (2) Animals were injected 30 min before cat exposure and tested 1 week later	Adamec *et al.*, 1997
		Elevated plus-maze	Rats	0.01–1	s.c., 45	+		Costall *et al.*, 1991

			Mice	0.01	i.p., 30	+		Holladay *et al.*, 1995
			Sprague-Dawley rats (180–230 g)	0.01–1	i.p., 30	o		Griebel *et al.*, 1997a
			DBA/2 mice (12–15 weeks)	0.001–1	i.p., 30	o		Johnson and Rodgers, 1996
			Female Wistar rats (200–250 g)	0.1	s.c., 30	+		Matto *et al.*, 1997b
		Free-exploration test	BALB/c mice (10 weeks)	0.01–1	s.c., 40	o		Belzung *et al.*, 1994
		Light/dark test	BALB/C mice (10 weeks)	0.01–1	s.c., 40	+		Belzung *et al.*, 1994
			Mice	0.0001–30	s.c., 40	+		Costall *et al.*, 1991
			Mice	1	s.c., 2–12 hr	+		Costall *et al.*, 1991
			Albino mice (Bradford-strain, 20–30 g)	0.0001–30	s.c., 40	+		Hughes *et al.*, 1990
			BALB/c mice (7 weeks old)	0.01–3	i.p., 30	o		Griebel *et al.*, 1997a
		Mouse defense test battery	Swiss mice (10 weeks old)	0.001–0.01, 1	i.p., 30	+	Positive effects on flight behavior only	Griebel *et al.*, 1997a
		Punished drinking test	Sprague-Dawley rats (180–230 g)	0.001–1	i.p., 30	o		Griebel *et al.*, 1997a
		Punished lever pressing test	Wistar rats (400–500 g)	0.01–1	i.p., 30	o		Griebel *et al.*, 1997a
		Social interaction test	Rats	0.01–1	s.c., 45	+	High light unfamiliar condition	Costall *et al.*, 1991
PD135158 + alcohol withdrawal		Light/dark test	Mice	10	i.p.	(+)	Antagonism of the anxiogenic effects of alcohol withdrawal	Costall *et al.*, 1991
PD135158 + cocaine withdrawal		Light/dark test	Mice	10	i.p.	(+)	Antagonism of the anxiogenic effects of cocaine withdrawal	Costall *et al.*, 1991
PD135158 + diazepam withdrawal		Light/dark test	Mice	10	i.p.	(+)	Antagonism of the anxiogenic effects of diazepam withdrawal	Costall *et al.*, 1991
PD135158 + nicotine withdrawal		Light/dark test	Mice	10	i.p.	(+)	Antagonism of the anxiogenic effects of nicotine withdrawal	Costall *et al.*, 1991
PD135158 + pentagastrin (100 nM)		Acoustic startle reflex	Wistar rats (275–300 g)	0.01	Amygdala, 5	(+)	Rats received 60 startle stimuli (119 dB) prior to drug administration	Frankland *et al.*, 1997
Pentagastrin	CCK_B antagonist	Acoustic startle reflex	Wistar rats (275–300 g)	0.01–10 nM/ 0.5 μL	Amygdala, 5	—	Rats received 60 startle stimuli (119 dB) prior to drug administration	Frankland *et al.*, 1997
			Wistar rats (275–300 g)	0.01–10 nM/ 0.5 μL	Striatum, 5	o	Rats received 60 startle stimuli (119 dB) prior to drug administration	Frankland *et al.*, 1997
			Wistar rats (275–300 g)	0.01–10 nM/ 0.5 μL	Nucleus accumbens, 5	o	Rats received 60 startle stimuli (119 dB) prior to drug administration	Frankland *et al.*, 1997
			Wistar rats (275–300 g)	10–100 nmol/ 5 μL	i.c.v., 5	—	Rats received 60 startle stimuli (119 dB) prior to drug administration and 180 startle stimuli during the test session	Frankland *et al.*, 1996

(*continued*)

TABLE 1. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
			Rats	0.01–10 nmol/5 μL	Amygdala, 0	—		Josselyn *et al.*, 1995b
			Rats	1–10 nmol/5 μL	i.c.v., 0	o		Josselyn *et al.*, 1995b
		Elevated plus-maze	Hooded Lister rats (200–250 g)	0.08–8/rat	i.c.v., 15	—		Singh *et al.*, 1991a
			Hooded Lister rats (200–250 g)	0.3–10 nmol/5 μL	i.c.v., 15	—		Singh *et al.*, 1991c
			TO mice (25–30 g)	0.8–8/5 μL	i.c.v., 15	—		Singh *et al.*, 1991b
		Food intake in hungry sheep	Castrated male sheep (whethers)	64–1020 pmol/min/3 hr	i.c.v.	—	Food intake was reduced and injections produced foot-stamping and vocalizations	Della-Fera and Baile, 1979
			Adult male and female Clung forest sheep	4–10 μg	i.c.v., 2	o		Ebenezer and Parrott, 1996
		Geller-Seifter conflict test	Hooded Lister rats (200–250 g)	16 μg/rat	i.c.v., 15	—	A VI30/FR5 schedule was used	Singh *et al.*, 1991a
		Light/dark test	TO mice (20–25 g)	0.8–8 nmol/mouse	i.c.v., 15	—		Singh *et al.*, 1991a
			TO mice (25–30 g)	0.8–8 nmol/5 μL	i.c.v., 15	—		Singh *et al.*, 1991b
Pentagastrin + CI-988 (1 mg/kg)		Elevated plus-maze	TO mice (25–30 g)	0.8 nmol/5 μL	i.c.v., 15	(+)		Singh *et al.*, 1991b
		Light/dark test	TO mice (25–30 g)	0.8 nmol/5 μL	i.c.v., 15	(+)		Singh *et al.*, 1991b
Proglumide	CCK_A antagonist	Elevated plus-maze	Outbred female mice (20–25 g)	0.1–10	i.p., 25	o		Vasar *et al.*, 1994a
		Exploratory behaviors	Swiss-Webster mice (20–25 g)	0.1–100	i.p., 5	o	Mice were confronted with a novel fringed cardboard object	Crawley *et al.*, 1986
Proglumide + CCK_8 (0.0025 mg/kg)	CCK_A antagonist	Elevated plus-maze	Outbred female mice (20–25 g)	0.1–10	i.p., 25	—	Potentiation of the anti-exploratory effects of CCK-8 (probably nonspecific effects)	Vasar *et al.*, 1994a
Proglumide + CCK_{8s} (1 fmol)	CCK_A antagonist	Four-hole box	Sprague-Dawley rats (200–220 g)	20/μg/1 μL	Median nucleus accumbens, 0	(+)		Daugé *et al.*, 1989a
Proglumide + CCK_{8s} (5 μg)	CCK_A antagonist	Exploratory behaviors	Swiss-Webster mice (20–25 g)	0.1–100	i.p., 5	(+)	Mice were confronted with a novel fringed cardboard object	Crawley *et al.*, 1986
SR 27897B	$CCK_{A/B}$ antagonist	Elevated zero-maze	Female Wistar rats (200–250 g)	0.01–2	i.p., 30	o		Matto *et al.*, 1997b
Suc-Trp-N(Me)-Nle-Asp-Phe-NH_2	CCK_B agonist	Operant food intake	Prepubertal Large White pigs (35–40 kg)	0.5–5 μg	i.v., 5	o		Ebenezer and Parrott, 1996
			Prepubertal Large White pigs (35–40 kg)	1–5 μg	i.c.v., 5	o		Ebenezer and Parrott, 1996
Transgenic rats	CCK_A receptor gene knockout	Open-field	OLETF and LETO rats (4 weeks)			—	Rats lacking CCK_A receptors displayed reduced locomotor and rearing activities	Kobayashi *et al.*, 1996

[1]+, anxiolysis; o, inactive; —, anxiogenesis; (+), antagonism of anxiogenic-like effects; (–), antagonism of anxiolytic-like effects.

BDNL, Boc-Tyr(SO_3H)-Nle-Gly-Trp-Nle-Asp-Phe-NH_2; BOC, butyl-oxycarbonyl; DLH, DL-homocysteic acid; DPAG, dorsal periaqueductal gray; FR, fixed ratio; i.c.v., intracerebroventricular; PTZ, pentylenetetrazole; SSRI, selective 5-HT reuptake inhibitor; VI, variable interval.

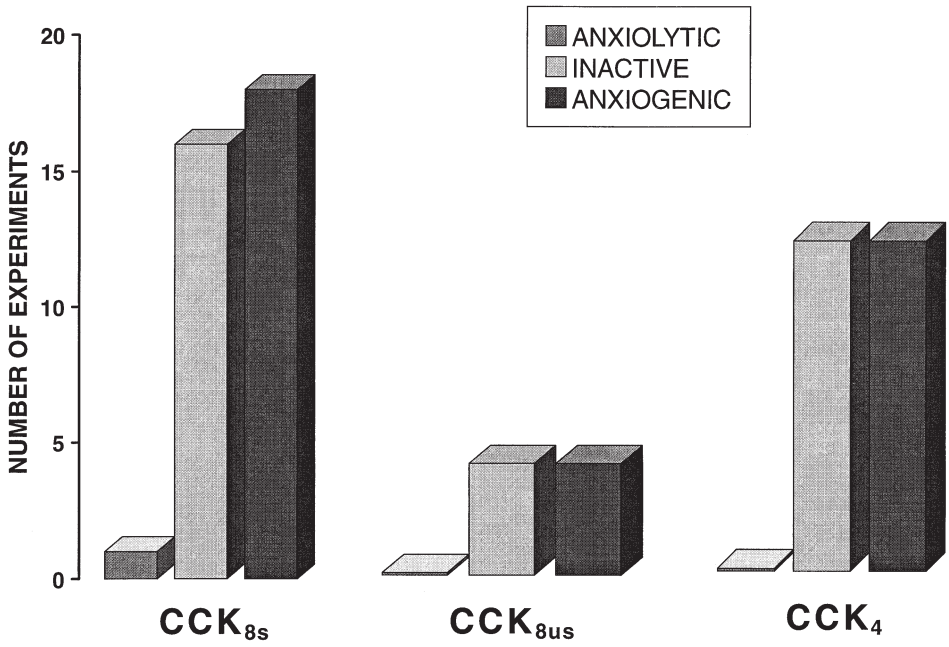

FIGURE 2. Illustration of the outcome of the three CCK fragments in animal models of anxiety.

Bíró and colleagues (1993, 1997) showed that pretreatment with inactive doses of the nonselective dopaminergic receptor antagonist haloperidol, the muscarinergic blocker atropine, the opiate receptor antagonist naloxone, the nonselective CRF receptor antagonist α-helical CRF_{9-41}, but not the β-adrenoceptor antagonist propranolol, the α-adrenoceptor antagonist phenoxybenzamine, the $GABA_A$ receptor antagonist bicuculline, and the nonselective 5-HT receptor antagonist methysergide, blocked the anxiogenic-like effects of CCK_{8s}. Furthermore, the anxiogenic-like action of CCK_4 was prevented by the 5-HT_{1A} receptor full agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (Rex *et al.*, 1997), but not by the 5-HT reuptake inhibitor citalopram or the norepinephrine (NE) reuptake inhibitor desipramine (Matto *et al.*, 1997a). The finding that 8-OH-DPAT blocked the CCK_4 potentiation of increase of 5-HT release produced by exposure to the elevated plus-maze led to the suggestion that CCK may interact with 5-HT_{1A} mechanisms via an influence on cortical 5-HT release (Rex *et al.*, 1997). Although these results do not permit us to draw a clear picture of the precise mechanisms underlying the anxiogenic-like activity of CCK, they indicate that multiple neurotransmitter systems (i.e., dopamine, acetylcholine, opiate, 5-HT, and CRF) may participate in these effects.

2.1.2. Behavioral effects of nonpeptide cholecystokinin receptor ligands in animal models of anxiety. CCK pharmacology is by far the leader in the development on nonpeptide receptor ligands, with an extreme degree of selectivity between the two receptor subtypes. Although a few CCK receptor agonists have been discovered, the development of selective antagonists has been of much greater importance (for reviews, see Bourin *et al.*, 1996; Van Megen *et al.*, 1996; Betancur *et al.*, 1997).

In spite of the predominant role suggested for the CCK_B receptor in anxiety, numerous studies have investigated the behavioral effects of CCK_A receptor antagonists in anxiety tests (Table 1). Figure 3 shows the most extensively studied CCK receptor antagonists in animal models of anxiety. They comprise several selective CCK_B receptor antagonists, including the BZ derivative L-365,260, the peptoids CI-988 and PD 135158, and the diphenyl-pyrazolidinone LY288513, and the CCK_A receptor antagonist devazepide. As shown in Fig. 4, results obtained with devazepide and L-365,260 have been highly variable. Both compounds produced anxiolytic-like effects in about one-half of the experiments. While devazepide was inactive in the remainder, it is noteworthy that one study reported that L-365,260 displayed anxiogenic-like activity in the elevated plus-maze after repeated treatment (Vasar *et al.*, 1997). Although results obtained with CI-988 in anxiety models have been less inconsistent, 26% of the experiments failed to reveal a significant modification in the behavioral baselines after CI-998 administration. Importantly, the magnitudes of the anxiolytic-like effects reported with CI-988 and L-365,260 generally were smaller in comparison to BZs and were not dose-dependent.

The reasons for this variability in drug effect remain largely unknown, but certainly include many factors, such as procedures, species, strain, gender, housing conditions, prior handling, level of illumination, and scoring technique, that do not necessarily become clear, even with close scrutiny of published reports (Bourin *et al.*, 1996; Johnson and Rodgers, 1996; Van Megen *et al.*, 1996; Griebel *et al.*, 1997a). For example, it has been suggested that models based on spontaneous or exploratory behaviors are more suitable for the investigation of CCK receptor antagonists than tests based on punished responses (Bourin *et al.*, 1996; Van Megen *et al.*, 1996). However, these compounds

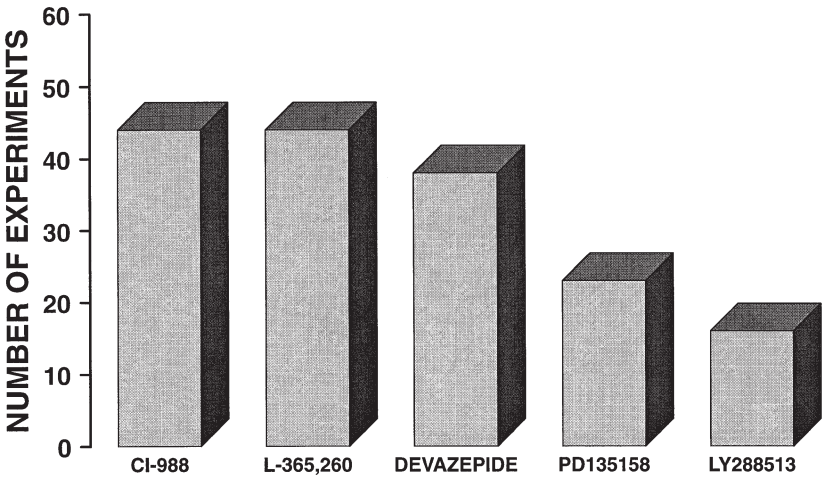

FIGURE 3. Studies of CCK receptor antagonists in anxiety models.

have been reported to have anxiolytic-like effects or no effect in both types of paradigms. These inconsistencies in drug profiles prompted Johnson and Rodgers (1996) to characterize fully the behavioral effects of several CCK receptor antagonists in the murine elevated plus-maze to detect subtle or minor changes in behavior that cannot be observed when only the usual spatiotemporal measures are recorded. Particular attention was paid to behavioral measures such as risk assessment related to the defensive repertoire. This latter concept refers to a pattern of responses (scanning, stretch attend, flat back approach) invariably observed in potentially dangerous situations (Blanchard *et al.*, 1991). In the plus-maze, the most prominent risk assessment measure is the stretched attend posture, a behavior that has been of particular interest, as it has been shown to be more sensitive to the effects of classical (i.e., BZ receptor ligands) and atypical (i.e., 5-HT_{1A} receptor ligands) anxiolytics than are the traditional indices of anxiety (Rodgers and Cole, 1994; Griebel *et al.*, 1997b). Results showed that despite detailed analysis, no effects were found after the administration of several CCK receptor antagonists (i.e., L-365,260, PD 135,158, or devazepide).

In this context, it was argued that classical animal models of anxiety are less sensitive to the action of CCK compounds that may be involved in a type of anxiety that is not assessed in these tests (Charrier *et al.*, 1995; Jenck *et al.*, 1996; Johnson and Rodgers, 1996). Most of these tests have been validated pharmacologically by BZs, which represent the first-choice treatment in generalized anxiety disorders (GADs), and this raises the question of whether routine models are suitable to screen CCK receptor antagonists. As a result, several novel test procedures have been developed that claim to model anxiety disorders other than GAD, such as panic disorder (Fontana and Commissaris, 1988; Fontana *et al.*, 1989; Graeff, 1991; Hendrie and Neill, 1991; Martin, 1993; Jenck *et al.*, 1995; Molewijk *et al.*, 1995; Griebel *et al.*, 1996). For example, it was demonstrated that rat-elicited flight responses in Swiss mice may serve as an

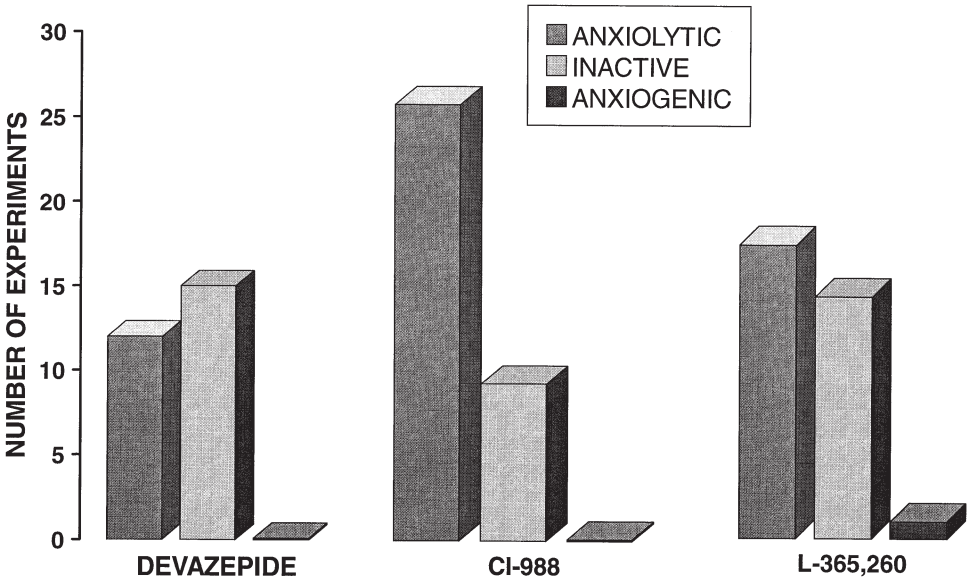

FIGURE 4. Illustration of the outcome of the three most extensively studied CCK receptor antagonists in animal models of anxiety.

experimental model for the screening of panic-modulating compounds, as it meets criteria for face validity and predictive validity, normally applied to such models (Griebel *et al.*, 1996). Furthermore, the aversion induced by electrical stimulation of the dorsal periaqueductal gray matter has been described as a realistic model of panic disorder, as it produces behavioral reactions that are reminiscent of panic signs (Jenck *et al.*, 1996). The behavioral effects of several CCK_B receptor antagonists have been investigated in these procedures. Results showed that L-365,260, PD 135158, LY288513, but not CI-988, produced a profile that may be consistent with an anti-panic-like action (Jenck *et al.*, 1996; Griebel *et al.*, 1997a). The lack of effects observed following administration of CI-988 was ascribed to the poor brain penetration of this compound in rats (Jenck *et al.*, 1996).

Taken together, the results observed with CCK receptor antagonists in classical animal models of anxiety do not convincingly establish the anxiolytic potential of these compounds. Although procedures that may model certain aspects of human panic appear to be more reliable tools when screening these compounds, further studies evaluating the action of CCK receptor antagonists in these tests are required. Information from clinical trials should permit future experimental research in this area to focus more precisely on the behavioral tests that are particularly sensitive to the effects of CCK receptor antagonists. However, as will be discussed in the following section, in clinical studies, the picture is even less clear.

2.1.3. Cholecystokinin receptor ligands in human studies. Although there is some evidence that systemic administration of CCK agonists elicits panic-like symptoms in healthy volunteers and patients with social phobia, and potentiates the occurrence of panic attacks in panic disorder patients, and that CCK_B receptor antagonists are able to block these effects (Bourin *et al.*, 1996; Van Megen *et al.*, 1996; Van Vliet *et al.*, 1997), the clinical trials that have been undertaken with L-365,260 and CI-988 in panic and CI-988 in GAD have been unsuccessful. Although the drugs were well tolerated, these studies failed to detect clinically significant differences between drug and placebo (Adams *et al.*, 1995; Kramer *et al.*, 1995; Pande, 1997). The authors of these publications discussed several possible reasons that may account for these negative findings, such as the poor pharmacokinetic characteristics of the drugs tested or the use of inadequate dosage. Clearly, further clinical trials with CCK_B receptor antagonists are needed before any definitive conclusion can be drawn regarding the potential of these compounds in the treatment of anxiety disorders.

In conclusion, despite intensive preclinical research effort, the role of CCK in the modulation of anxiety remains controversial, with inconsistent and sometimes conflicting effects observed in animals, and with a lack of anxiolytic activity of CCK_B receptor antagonists reported in humans. Reasons for such discrepancies are not fully understood, but certainly include many factors, such as animal models and inappropriate pharmacokinetics of the drugs. In addition, it is unlikely that stimulation of CCK receptors by itself is the final common pathway leading to anxiety. More probably, CCK induces its effects on anxiety by interactions with other neuronal systems.

2.2. *Corticotropin-Releasing Factor*

CRF is a 41-residue peptide originally isolated from ovine hypothalamus by Vale and colleagues (1981). Sequences for human and rat CRF subsequently were determined and found to be identical to each other, and they differed from ovine CRF in 7 of the 41 amino acid residues (Rivier *et al.*, 1983). Two nonmammalian CRF-related peptides, sauvagine and urotensin I, have been isolated from the caudal neurosecretory system of three species of teleost fishes and from the skin of the frog *Phyllomedusa sauvagei*, respectively (Erspamer and Mechiorri, 1980; Ichikawa *et al.*, 1982; Lederis *et al.*, 1983; McMaster *et al.*, 1988). Both peptides share a considerable sequence homology (50%) with CRF. CRF is widely distributed in the brain, with highest concentrations found in the hypothalamus, where it is produced and secreted by the parvocellular neurons of the hypothalamic paraventricular nucleus (PVN). It is the major hypophysiotropic factor regulating basal and stress-induced release of adrenocorticotropic hormone (ACTH), β-endorphin, and other proopiomelanocortin-derived peptides (Vale *et al.*, 1981, 1983). Moderate and low levels of CRF are also present in cortical and limbic structures, respectively (Orth, 1992).

The effects of CRF are mediated by two specific G-protein-coupled seven-transmembrane domain receptors called CRF_1 and CRF_2 (Chalmers *et al.*, 1995; De Souza, 1995). Recently, two splice variants of the CRF_2 receptor ($CRF_{2\alpha}$ and $CRF_{2\beta}$) have been characterized in the rat brain (Lovenberg *et al.*, 1995). Tissue distribution analysis showed that CRF_1 receptor expression is most abundant in neocortical, cerebellar, and limbic structures, whereas CRF_2 receptor expression is generally localized in subcortical structures, notably in the lateral septum and various hypothalamic areas (Chalmers *et al.*, 1995). Examination of CRF_2 receptor splice variants indicates that $CRF_{2\alpha}$ is primarily expressed within the brain and the $CRF_{2\beta}$ variant is found in both the CNS and periphery (Lovenberg *et al.*, 1995). This anatomical information provided a basis for functional hypotheses related to CRF receptor subtypes, and suggested that CRF may contribute significantly both to behavioral responses to stress and to emotional behavior itself (Koob, 1991).

2.2.1. Behavioral effects of central application of corticotropin-releasing factor in animal models of anxiety and stress. A vast literature indicates that intracerebroventricular administration of CRF, which presumably increases the concentrations of CRF in the CNS, produces physiological and behavioral alterations virtually identical to those observed in laboratory animals in response to stress, including increases in heart rate and mean arterial pressure, changes

in gastrointestinal function, suppression of exploratory behavior, induction of grooming, reduction of feeding and food intake, and disruption of reproductive behavior. Further actions of centrally administered CRF include the potentiation of acoustic startle responses, the facilitation of fear conditioning, and the enhancement of shock-induced freezing and fighting behavior (Table 2). Importantly, these effects are not observed after systemic administration of CRF (Sutton *et al.*, 1982; Britton *et al.*, 1984; Sherman and Kalin, 1986; Bueno and Gué, 1988; Insel and Harbaugh, 1989; Takahashi *et al.*, 1989; Becker and Hennessy, 1993) and are not blocked by hypophysectomy (Morley and Levine, 1982; Lenz *et al.*, 1988b; Berridge and Dunn, 1989; Gué *et al.*, 1991; Adamec and McKay, 1993; McKay and Adamec, 1993), vagotomy (Lenz *et al.*, 1988a; Mönnikes *et al.*, 1992a), adrenalectomy (Hagiwara *et al.*, 1986; Lenz *et al.*, 1988a), or pretreatment with dexamethasone (Britton, D. R. *et al.*, 1984, 1986; Britton, K. T. *et al.*, 1986a), suggesting that these actions of CRF do not involve activation of the pituitary-adrenal axis, but are mediated by CRF receptors present in the CNS. This idea is further supported by the finding that the nonselective CRF receptor antagonists α-helical $CRF_{9–41}$ and D-Phe $CRF_{12–41}$ were found to reverse the behavioral effects of exogenously administered CRF (Table 2).

As part of an effort to delineate the neural circuitry underlying intracerebroventricular CRF effects, several studies have examined the action of direct administration of CRF into local brain areas and the influence of specific brain lesions on the effects of CRF. Several of the effects of CRF seem to be mediated by activation of the central NE system. Microinjection of CRF directly into the locus coeruleus of rats has been found to produce defensive withdrawal responses from a novel environment (Butler *et al.*, 1990), to reduce drinking behavior in a brightly illuminated area (Weiss *et al.*, 1994), and to disrupt gastrointestinal function (Mönnikes *et al.*, 1992b). Similarly, intra-amygdala infusion of CRF has been reported to produce anxiogenic-like behavior in the open-field test and increase grooming in rats (Liang and Lee, 1988; Lee and Tsai, 1989; Elkabir *et al.*, 1990). However, increases in anxiety-related reactions have not been obtained systemically, as was shown by the lack of effect of intra-amygdala infusion of CRF in the acoustic startle test in rats (Liang *et al.*, 1992a). Moreover, lesion of the amygdala failed to block the anxiogenic-like effects of intracerebroventricular CRF in the acoustic startle test (Lee and Davis, 1995, 1997b), whereas it completely antagonized these effects in the fear-potentiated startle procedure (Liang *et al.*, 1992b). To explain these discrepancies, it was suggested that the use of different lesion techniques (electrolytic vs. chemical) may be important (Lee and Davis, 1997b). Alternatively, it was proposed that the acoustic startle test may relate to a type of anxiety that does not primarily involve the amygdala (Lee and Davis, 1997b).

The hypothalamic PVN has also been suggested to be implicated in the anxiogenic-like effects of CRF. Injection of antibodies to CRF in the PVN has been found to block the increase in anxiety-related responses in the elevated plus-maze produced by social defeat (Menzaghi *et al.*, 1992). In addition, injection of CRF into the PVN has been reported to increase self-grooming (Krahn *et al.*, 1988). However, in another study, lesions of the PVN failed to block the anxiogenic-like effects of CRF in the acoustic startle test (Liang *et al.*, 1992a). Taken together, these results do not allow a precise delineation of the neural mechanism that may underlie the anxiogenic-like effects of intracerebroventricular CRF. The reasons for this variability remain unclear. It is possible that the use of different experimental procedures (e.g., acoustic and fear-potentiated startle reflex, open-field) may explain, at least in part, these discrepancies. In these tests, different facets of anxiety- and/or stress-oriented reactions (e.g., startle, grooming, defensive withdrawal, decrease in exploratory activity, and colonic transit) can be measured. Hence, it is conceivable that different neural circuits may be involved in these responses.

2.2.2. Behavioral effects of corticotropin-releasing factor inhibition or corticotropin-releasing factor overexpression using molecular biological techniques in animal models of anxiety. Two recent studies using CRF transgenic mouse lines overexpressing CRF further emphasized the anxiogenic properties of CRF, since these mice exhibited a behavioral state resembling that produced by anxiety (Stenzel-Poore *et al.*, 1996; Koob and Gold, 1997). In another study with CRF knock-out mice, no difference in the anxiety-like behaviors was observed between mutant and wild-type mice. However, compensation by other peptidergic and aminergic mechanisms may have occurred (Miczek, 1997). Central injection of an antisense oligonucleotide directed against the CRF gene in rats has been reported to increase exploratory activity in the open-field test and discriminative avoidance responses in the shuttle-box, effects that may be consistent with an anxiolytic-like action (Skutella *et al.*, 1994; Wu *et al.*, 1997). Molecular biological techniques have also been used to examine the importance of each of the CRF receptor subtypes in the anxiogenic-like effects of CRF. Based on the findings that the endogenous peptides urocortin and urotensin, which display high affinity to both CRF_1 and CRF_2 receptors, but bind preferentially to the CRF_2 subtype, mimicked the effects of CRF in animals (Spina *et al.*, 1996; Jones *et al.*, 1997; Moreau *et al.*, 1997), it was proposed that the anxiogenic-like effects of CRF may primarily involve CRF_2 receptors. However, intracerebroventricular injection of mRNA antisense oligonucleotides to the CRF_1, but not to the CRF_2, receptor has been shown to produce anxiolytic-like activity in the defensive withdrawal test in rats (Heinrichs *et al.*, 1997). Moreover, reductions in anxiety-related behavior were observed after chronic infusion of CRF_1 receptor antisense oligonucleotides into the central nucleus of the amygdala (Liebsch *et al.*, 1995). Taken together, these latter findings suggest that the CRF_1 receptor subtype might represent the

TABLE 2. Effects of Drugs Modulating the CRF System in Animal Models of Anxiety

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
D-phe CRF_{12-41}	$CRF_{1/2}$ antagonist	Defensive withdrawal	Wistar rats (365–435 g)	0.2–5 μg/0.5 μL	i.c.v., 5	+	Experiments were performed in an open-field containing a cylindrical chamber	Rodriguez de Fonseca *et al.*, 1996
			Wistar rats (365–435 g)	5 μL	i.c.v., 5	+	(1) Experiments were performed in an open-field containing a cylindrical chamber (2) Animals were exposed to swim stress	Rodriguez de Fonseca *et al.*, 1996
		Elevated plus-maze	Wistar rats (300–400 g)	5–25 μg	i.c.v., 60	o		Menzaghi *et al.*, 1994
		Isolation-induced behavioral changes	Preweaning guinea-pigs (4–6 and 20–26 days)	15–150 μg	s.c., 0	?	Vocalizing was increased	Hennessy *et al.*, 1997
		Social defeat + elevated plus-maze	Wistar rats (300–400 g)	1–25 μg	i.c.v., 5	+		Menzaghi *et al.*, 1994
		Stress-induced delay in gastric emptying	Sprague-Dawley rats (200–240 g)	2.6 nmol/10 μL	Intracisternal, 180	+	Stress was induced by abdonimal surgery	Hernandez *et al.*, 1993
D-Phe CRF_{12-41} + HU-210 (20 μg, cannabinoid)		Defensive withdrawal	Wistar rats (365–435 g)	5 μg/5 μL	i.c.v., 5	(+)	Tests were performed in an open-field containing a cylindrical chamber	Rodriguez de Fonseca *et al.*, 1996
D-Phe CRF_{12-41} + NPY (1 μg)		Operant conflict paradigm	Rats	0.2–5 μg	i.c.v.	+	Potentiation of the anxiolytic-like effects of NPY	Britton *et al.*, 1997a
α-Helical CRF_{9-41}	$CRF_{1/2}$ antagonist	Acoustic startle reflex	Wistar rats (200–220 g)	25 μg/2 μL	i.c.v., 5	o	Rats were presented with 5 118-dB white noise bursts	Swerdlow *et al.*, 1989
		Acquisition of conditioned emotional response	Rats	1–25 μg/5 μL	i.c.v., 30	+	Four pairings of a light stimulus and 0.5 sec, 2.1 mA footshock were presented	Cole *et al.*, 1987
		Colonic function	Female Sprague-Dawley rats (150–200 g)	50 μg	i.c.v.	+	Wrapping restraint stress was used	Williams *et al.*, 1987
			Female Sprague-Dawley rats (150–200 g)	50 μg	i.v.	+	Wrapping restraint stress was used	Williams *et al.*, 1987
		Defensive burying	Wistar rats			+		Korte *et al.*, 1994
		Defensive withdrawal	Sprague-Dawley rats (230–335 g)	20 μg/2 μL	i.c.v., 20	+	The drug reduced the latency to emerge in an unfamiliar open-field	Takahashi *et al.*, 1989
			Sprague-Dawley rats (305 g)	20 μg/1 μL	i.c.v., 20	+	Animals were exposed to an open-field containing odors of stressed conspecifics	Takahashi *et al.*, 1990
			Rats	20 μg	i.c.v., 20	+	Experiments were performed in an open-field containing a darkened compartment	Takahashi and Kalin, 1989

(*continued*)

TABLE 2. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
			Rats	20 μg	i.c.v., 20	+	Experiments were performed in an open-field contained urine and feces collected from a stressed (footshocks) conspecific	Takahashi and Kalin, 1989
		Elevated plus-maze	Wistar rats (200–250 g)	50–100 μg	i.c.v., 60	+		Adamec *et al.*, 1991
			BALB/c mice (20 g)	20–50 μg/5 μL	i.c.v., 60	+		Conti *et al.*, 1994
			Wistar rats (300–400 g)	5–25 μg	i.c.v., 60	—		Menzaghi *et al.*, 1994
			Wistar rats (200–250 g)	50 μg	i.c.v., 60	o	Rats were stressed with repeated handling	Adamec *et al.*, 1991
			Wistar rats (200–220 g)	5–50 μg/5 μL	i.c.v., 30	o		Baldwin *et al.*, 1991
			Wistar rats (200–250 g)	0.001–1 μg/2 μL	i.c.v., 60	o		Bíró *et al.*, 1993
			NIH mice (20 g)	25–50 μg/5 μL	i.c.v., 60	o		Conti *et al.*, 1994
			CD mice (20 g)	20–50 μg/5 μL	i.c.v., 60	o		Conti *et al.*, 1994
			CF-1 mice (20 g)	25–50 μg/5 μL	i.c.v., 60	o		Conti *et al.*, 1994
			Wistar rats (200–250 g)	0.5 μg/0.5 μL	DPAG, 10	o		Martins *et al.*, 1997
			Wistar rats (200–220 g)	250–500 ng/0.5 μL	Amygdala, 30	o		Rassnick *et al.*, 1993
		Exploratory behavior following restraint stress	CD-1 mice (25–35 g)	10–50 μg/4 μL	i.c.v., 45	+	The drug increased the time spent in contact with novel stimuli	Berridge and Dunn, 1987a
		Footshock-induced freezing	Rats	25 μg	i.c.v., 24	+	Rats received footshocks of 1 mA, 1 sec each, 20 sec apart	Sherman *et al.*, 1987
		Geller-Seifter conflict test	Rats	1–25 μg/5 μL	i.c.v., 30	+	Random interval 60-sec schedule	Koob, 1991
			Wistar rats (200–250 g)	25–200 μg	i.c.v., 30	o		Britton, K. T. *et al.*, 1986b
		Hole-board	Wistar rats (200–250 g)	50 μg	i.c.v., 60	+	Rats were stressed with repeated handling and surgery	Adamec *et al.*, 1991
		Isolation-induced behavioral changes	Preweaning guinea-pigs	25 μg/5 μL	i.c.v. (cannula), 90	+	Vocalizing was increased	Hennessy *et al.*, 1992
			Preweaning guinea-pigs	50 μg	s.c., 0	?	Vocalizing and locomotor activity was increased	McInturf and Hennessy, 1996
		Mental stress-induced colonic motor alteration	Sprague-Dawley rats (350–500 g)	5 μg/5 μL	i.c.v., 30	o	Rats received 6 series of electric footshocks (1.5 mA, 180 msec)	Gué *et al.*, 1991
		Open-field	Wistar rats (310–330 g)	5 μg/5 μL	i.c.v., 30	o		Kumar and Karanth, 1996
			BALB/c mice (10 weeks)	0.8–8 nmol	i.c.v., 30	o		Moreau *et al.*, 1997
		Phenylephrine-induced defensive withdrawal	Sprague-Dawley rats (250–300 g)	25–50 μg	i.c.v., 20	+	The drug decreased pattern of defensive withdrawal	Yang *et al.*, 1990
		Potentiated startle reflex	Wistar rats (200–260 g)	0.1–0.3 μg	Intracaudal pontine reticular nucleus, 5	+	Unconditioned stimulus was a 0.6-mA footshock	Fendt *et al.*, 1997

	Wistar rats (200–220 g)	5–25 μg/2 μL	i.c.v., 5	+	Startle reflex was potentiated by pairing 65-dB sound and 0.4-mA footshocks	Swerdlow *et al.*, 1989
Rat pup isolation calls	Sprague-Dawley rats (5–6 days old)	1 μg/1 μL	i.c.v., 0	?	Vocalizing was increased	Insel and Harbaugh, 1989
Restraint-induced decrease in investigatory behavior	Mice	10–50 μg	i.c.v., 10	+	Testing was performed in a multicompartment chamber	Berridge and Dunn, 1987b
Restraint-induced defensive withdrawal	Sprague-Dawley rats (300–350 g)	1 μg/300 nL	Locus coeruleus, 40	+		Smagin *et al.*, 1996
	Sprague-Dawley rats (250–300 g)	25 μg	i.c.v., 20	+	The drug decreased pattern of defensive withdrawal	Yang *et al.*, 1990
Shock-induced freezing	Sprague-Dawley rats (250–400 g)	20 μg/2 μL	i.c.v., 20	+	Rats received 3 1-sec footshocks (0.79 mA) at 20-sec intervals	Kalin and Takahashi, 1990
	Sprague-Dawley rats (180–200 g)	25 μg	i.c.v., 20	+	Rats received 3 1-sec footshocks (0.79 mA) at 20-sec intervals	Kalin *et al.*, 1988
	Sprague-Dawley rats (180–200 g)	25 μg	i.c.v., 40	o	Rats received 3 1-sec footshocks (0.79 mA) at 20-sec intervals	Kalin *et al.*, 1988
Social defeat + elevated plus-maze	Wistar rats (275–325 g)	5–25 μg	i.c.v., 5	+	Antagonism of the anxiogenic effects of social defeat	Heinrichs *et al.*, 1992
	Wistar rats (275–325 g)	125–500 ng	Amygdala, 0	+	Antagonism of the anxiogenic effects of social defeat	Heinrichs *et al.*, 1992
	Wistar rats (300–400 g)	25 μg	i.c.v., 5	+		Menzaghi *et al.*, 1994
	Squirrel monkeys (800–1200 g)	10 μg/10 μL	i.c.v., 5	—		Winslow *et al.*, 1989
Stress-induced accelerated colonic transit	Sprague-Dawley rats (300–350 g)	13 nmol/rat	Paraventricular nucleus, 15	+	Stress was induced by avoiding water by standing on a small cube	Mönnikes *et al.*, 1993
Stress-induced alteration in colonic function	Sprague-Dawley rats (290–370 g)	13 nmol/100 nL	Paraventricular nucleus, 60	+	Animals were subjected to restraint stress	Mönnikes *et al.*, 1992a
Stress-induced c-fos expression and fecal output	Sprague-Dawley rats (250–300 g)	50 μg/10 μL	i.c.v., 10	+	Stress was induced by avoiding water by standing on a small cube	Bonaz and Taché, 1994
Stress-induced decrease in food intake	Sprague-Dawley rats (300–350 g)	50 μg/5 μL	i.c.v., 60	+	Animals were subjected to restraint	Krahn *et al.*, 1986
Stress-induced delay in gastric emptying	Sprague-Dawley rats (200–240 g)	13 nmol/10 μL	Intracisternal, 180	+	Stress was induced by abdominal surgery	Hernandez *et al.*, 1993
Stress-induced fighting	Wistar rats (180–200 g)	5–25 μg/2 μL	i.c.v., 5	+	Pair of rats were exposed to inescapable footshocks (0.6 mA)	Tazi *et al.*, 1987
Stress-induced freezing	Sprague-Dawley rats (180–220 g)	25–50 μg	i.c.v., 20	+	Rats received 3 brief (1.0 sec) footshocks at 20-sec intervals	Kalin *et al.*, 1988
	Sprague-Dawley rats (300–350 g)	50–100 ng/1 μL	Central amygdaloid nucleus, 3	+	Freezing was induced by 3 footshocks of 1 mA/1 sec and animals tested immediately thereafter	Swiergiel *et al.*, 1993

(*continued*)

TABLE 2. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
			Sprague-Dawley rats (300–350 g)	50–100 ng/1 μL	Central amygdaloid nucleus, 3	+	Freezing was induced by 3 footshocks of 1 mA/1 sec and animals tested 24 hr later	Swiergiel *et al.*, 1993
		Stress-induced gastrointestinal alterations	Sprague-Dawley rats (200–250 g)	10 μg/5 μL	i.c.v., 15	+	Rats were subjected to partial body restraint	Lenz *et al.*, 1988b
			Sprague-Dawley rats (200–250 g)	10 nmol	i.v., 45	o	Rats were subjected to partial body restraint	Lenz *et al.*, 1988b
		Stress-induced increase in locomotion	Wistar rats (300–420 g)	10 μg/2 μL	i.c.v., 0	+	Stress was induced by placing rats in water for 60 min	Morimoto *et al.*, 1993
		Stress-induced increase in paradoxical sleep	Sprague-Dawley rats (220–240 g)	100 μg/5 μL	i.c.v., 30	+		Gonzalez and Valatx, 1997
		Defensive withdrawal		20 μg/rat	i.c.v.	+		Weidemann *et al.*, 1996
		Social interaction test			i.c.v.	+		Weidemann *et al.*, 1996
α-Helical $CRF_{9–41}$ + BIBP3226 (5 μg, NPY_1 antagonist)		Elevated plus-maze	Wistar rats (330–380 g)	1 μg/5 μL	i.c.v., 60	(+)		Kask *et al.*, 1997
α-Helical $CRF_{9–41}$ + CCK_8 (1 μg)		Elevated plus-maze	Wistar rats (200–250 g)	0.001–1 μg/ 2 μL	i.c.v., 60	(+)		Bíró *et al.*, 1993
α-Helical $CRF_{9–41}$ + ethanol withdrawal		Elevated plus-maze	Wistar rats (200–220 g)	5-25 μg/5 μL	i.c.v., 30	(+)	Antagonism of the anxiogenic effects of ethanol withdrawal	Baldwin *et al.*, 1991
		Elevated plus-maze	Wistar rats (200–220 g)	250 ng/0.5 μL	Amygdala, 30	(+)	Antagonism of the anxiogenic effects of ethanol withdrawal	Rassnick *et al.*, 1993
		Elevated plus-maze	Wistar rats (200–220 g)	250 ng/0.5 μL	i.c.v., 30	—	No antagonism of the anxiogenic effects of ethanol withdrawal	Rassnick *et al.*, 1993
α-Helical $CRF_{9–41}$ + strychnine (0.75 mg/kg)		Acoustic startle reflex	Wistar rats (200–220 g)	25 μg/2 μL	i.c.v., 5	—	No antagonism of the anxiogenic-like effects of strychnine	Swerdlow *et al.*, 1989
Antalarmin	$CRF_{1/2}$ antagonist	Footshock-induced immobility	Rats	20	i.p.	+	Two inescapable footshocks of 1.0 mA, 5 sec each, were delivered	Spina *et al.*, 1997
Antisense ODN	Blockade of CRF_1 receptor translation	Defensive withdrawal	Wistar rats (300–350 g)	48 μg/24 μL/ day	i.c.v., for 5 days	+	Experiments were performed in an open-field containing a darkened compartment	Heinrichs *et al.*, 1997
	Blockade of CRF_2 receptor translation	Defensive withdrawal	Wistar rats (300–350 g)	48 μg/24 μL/ day	i.c.v., for 5 days	o	Experiments were performed in an open-field containing a darkened compartment	Heinrichs *et al.*, 1997
	CRF_1 inhibition	Elevated plus-maze	Wistar rats (300–350 g)	0.25 μg/0.5 μL/hr	Amygdala	+	Rats were subjected to social defeat before exposure to the plus-maze	Liebsch *et al.*, 1995

	CRF gene inhibition	Open-field	Sprague-Dawley rats (200–250 g)	1 nmol	Hippocampus, 4 injections	+	The treatment increased exploration	Wu *et al.*, 1997
	Blockade of CRF translation	Shuttle box conflict task	Sprague-Dawley rats (350–500 g)	5 μg/μL	i.c.v., 3 times	+	Rats displayed accelerated acquisition of an operant avoidance task	Skutella *et al.*, 1994
	Blockade of CRF_1 receptor translation	Swim stress + elevated plus-maze	Wistar rats (300–350 g)	48 μg/24 μL/day	i.c.v., for 5 days	o		Heinrichs *et al.*, 1997
	Blockade of CRF_2 receptor translation	Swim stress + elevated plus-maze	Wistar rats (300–350 g)	48 μg/24 μL/day	i.c.v., for 5 days	o		Heinrichs *et al.*, 1997
Astressin	$CRF_{1/2}$ antagonist	Stress-induced alterations in colonic motor function	Sprague-Dawley rats (250–280 g)	3–10 μg/5 μL	i.c.v., 10	+	Rats were put on a platform placed in the middle of a home cage filled with water	Martinez *et al.*, 1997
			Sprague-Dawley rats (250–280 g)	3–10 μg/5 μL	i.c.v., 160	+	Gastric emptying was induced by laparotomy and cecal manipulation (1 min)	Martinez *et al.*, 1997
CP-154,526	CRF_1 antagonist	Elevated plus-maze	Sprague-Dawley rats (200 g)	1	i.p., 30	+		Lundkvist *et al.*, 1996
			Sprague-Dawley rats (180–230 g)	0.62–20	i.p., 30	o		Griebel *et al.*, 1998
		Free-exploration test	BALB/c mice (7 weeks old)	5 and 20	i.p., 30	+	Weak effects	Griebel *et al.*, 1998
		Light/dark test	BALB/c mice (7 weeks old)	10–40	i.p., 30	+		Griebel *et al.*, 1998
		Mouse defense test battery	Swiss mice (10 weeks old)	5–20	i.p., 30	+	Flight, risk assessment and defensive biting were significantly reduced	Griebel *et al.*, 1998
		Potentiated startle reflex	Sprague-Dawley rats	10–17.8	i.p.	+	Animals were exposed to 108-dB acoustic startle stimuli	Schulz *et al.*, 1996
			Sprague-Dawley rats	17.8	p.o., 60	+	Animals were exposed to 108-dB acoustic startle stimuli	Chen *et al.*, 1997
		Punished lever pressing test	Wistar rats (400–500 g)	2.5–10	i.p., 30	o	Two VI schedules (VI30 sec for food, VI10 sec for shock) were used	Griebel *et al.*, 1998
		Vogel conflict test	Sprague-Dawley rats (180–230 g)	0.62–20	i.p., 30	o		Griebel *et al.*, 1998
CRF	Endogenous peptide	Acoustic startle reflex	Rats	10–40 ng	Intracaudal pontine reticular nucleus, 0	—	Rats received 120 startle stimuli of 105 dB	Birnbaum *et al.*, 1995
			Rats	1 μg	i.c.v.	—		Swerdlow *et al.*, 1985
			Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	—	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997a
			Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	—	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997b
			Sprague-Dawley rats (350–430 g)	1 μg/5 μL	Bed nucleus of the stria terminalis, 0	—	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997b

(*continued*)

TABLE 2. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
			Sprague-Dawley rats (280–340 g)	0.25 μg/5 μL	i.c.v., 30	—	Rats were pretreated with arginine vasopressin 48 hr before (30 pg)	Pelton *et al.*, 1997
			Sprague-Dawley rats (280–340 g)	0.25 μg/5 μL	i.c.v., 30	—	CRF was given after the delivery of a footshock (0.4 mA) 72 and 48 hr earlier	Pelton *et al.*, 1997
			Sprague-Dawley rats (350–430 g)	7.5–120 ng/ 0.5 μL	i.c.v., 0	o	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997a
			Sprague-Dawley rats (350–430 g)	1 μg/5 μL	Ventral hippocampus, 0	o	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997b
			Sprague-Dawley rats (280–340 g)	0.25 μg/5 μL	i.c.v., 30	o		Pelton *et al.*, 1997
		Chair-restrained monkeys	Rhesus monkeys	20–180 μg/ 200 μL	i.c.v.	—	The treatment increased behavioral arousal	Kalin, 1985
		Colonic function	Female Sprague-Dawley rats (150–200 g)	0.3–10 μg	i.c.v.	—	CRF inhibited intestinal transit and increased colonic transit	Williams *et al.*, 1987
			Female Sprague-Dawley rats (150–200 g)	0.3–10 μg	i.v.	—	CRF inhibited intestinal transit and increased colonic transit	Williams *et al.*, 1987
			Mongrel dogs (15–18 kg)	20–100 ng	i.c.v., 0	—	CRF suppressed gastric cyclic migrating motor complex	Bueno and Fioramonti, 1986
			Sprague-Dawley rats (290–370 g)	0.2–0.6 nmol/ 100 nL	Paraventricular nucleus, 60	—		Mönnikes *et al.*, 1992a
			Mongrel dogs (15–18 kg)	100–500 ng	i.v., 0	o		Bueno and Fioramonti, 1986
			Sprague-Dawley rats (290–370 g)	0.26–0.6 nmol/ 100 nL	Lateral hypothalamus, 60	o		Mönnikes *et al.*, 1992a
			Sprague-Dawley rats (290–370 g)	0.2–0.6 nmol/ 100 nL	Central amygdala, 60	o		Mönnikes *et al.*, 1992a
		Colonic transit	Sprague-Dawley rats (350–350 g)	50 nL	Locus coeruleus	—		Mönnikes *et al.*, 1992b
			Sprague-Dawley rats (350–350 g)	50 nL	Locus coeruleus	—	Experiments were performed on fasted rats	Mönnikes *et al.*, 1992b
		Conditioned stress response	Roman high-avoidance rats (280–370 g)	30 ng/1 μL	Amygdala, 10	?	(1) Immobility was decreased (2) Animals received an inescapable footshock (0.6 mA, 3 sec)	Wiersma *et al.*, 1997
			Roman low-avoidance rats (280–370 g)	30 ng/1 μL	Amygdala, 10	?	(1) Exploration was increased (2) Animals received an inescapable footshock (0.6 mA, 3 sec)	Wiersma *et al.*, 1997
		Conditioned suppression of responding	Rats (160–180 g)	0.5 μg/1 μL	i.c.v., 30	—		Cole and Koob, 1988
			Wistar rats (200–250 g)	0.5–1 μg/2 μL	i.c.v., 60	—		Britton *et al.*, 1988
		Conflict test	Sprague-Dawley rats (276–300 g)	0.1–1 μg/3 μL	i.c.v., 5	—	Rats were trained under a FR20 schedule	de Boer *et al.*, 1992

	White Carneau pigeons (1 year old)	30 μg/5 μL	i.c.v., 60	—	A multiple FR schedule was used	Zhang and Barrett, 1990
	White Carneau pigeons (1 year old)	10–30 μg/5 μL	i.c.v., 60	—	A multiple FR schedule was used	Barrett *et al.*, 1989
Defensive burying	Wistar rats	30 ng/1 μL	Amygdala, 10	—		Wiersma *et al.*, 1996
Defensive withdrawal	Sprague-Dawley rats (230–335 g)	300 ng/5 μL	i.c.v., 20	—	The drug increased pattern of defensive withdrawal	Takahashi *et al.*, 1989
	Sprague-Dawley rats (250–300 g)	50–100 ng	i.c.v., 25	—	The drug increased pattern of defensive withdrawal	Yang *et al.*, 1990
	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	—	The drug increased pattern of defensive withdrawal	Yang and Dunn, 1990
	Long-Evans rats (250–300 g)	0.1–1 μg/1.6 μL	Locus coeruleus, 45	—	Experiments were performed in an open-field containing a darkened compartment	Butler *et al.*, 1990
	Long-Evans rats (250–300 g)	1 μg/1.6 μL	Cerebral aqueduct, 45	—	Experiments were performed in an open-field containing a darkened compartment	Butler *et al.*, 1990
	Rats	300 ng	i.c.v., 20	—		Takahashi and Kalin, 1989
	Preweaning guinea-pigs	14 μg	s.c., 60	o	The latency to enter a dark chamber was measured	Becker and Hennessy, 1993
	Rats	300 ng	i.p., 20	o		Takahashi and Kalin, 1989
Elevated plus-maze	Wistar rats (200–220 g)	0.5 μg/2 μL	i.c.v., 30	—		Baldwin *et al.*, 1991
	Rats	2 μg	i.c.v.	—		McKay and Adamec, 1993
	Rats	100 ng	i.c.v.	—		File *et al.*, 1988
	Wistar rats (200–250 g)	1–2 μg	i.c.v., 60	—		Adamec *et al.*, 1991
	Wistar rats (200–220 g)	0.5 μg/2 μL	i.c.v., 30	—		Baldwin *et al.*, 1991
	Wistar rats (250–300 g)	2 μg/3 μL	i.c.v., 60	—		Adamec and McKay, 1993
	Wistar rats (220–250 g)	0.1 nmol/5 μL	i.c.v., 30	—		Moreau *et al.*, 1997
	Sprague-Dawley rats (250–275 g)	0.1–1 μg	i.c.v., 30	—		Jones *et al.*, 1997
	Sprague-Dawley rats	0.5 μg/5 μL	i.c.v., 20	—		Moy *et al.*, 1997
	Wistar rats (320–390 g)	4.9 μg	i.c.v., for 7 days	—		Buwalda *et al.*, 1997
	Wistar rats (200–250 g)	2 μg/1 μL	DPAG, 10	—		Martins *et al.*, 1997
	Rats	1–25 μg	i.c.v., 15	—		Behan *et al.*, 1995
	Wistar rats (200–250 g)	0.5-2 μg	i.c.v., 60	o	Rats were stressed with repeated handling	Adamec *et al.*, 1991
Exploratory behavior in a multicompartment chamber	CD-1 mice (25–35 g)	75 ng/4 μL	i.c.v., 10	—		Berridge and Dunn, 1986
	Sprague-Dawley rats (250–300 g)	25 ng	i.c.v., 10	—		Spadaro *et al.*, 1990
	Sprague-Dawley rats (250–300 g)	25 ng	Lateral ventricle, 10	—	Cerebral aqueduct was blocked with cold cream	Spadaro *et al.*, 1990
	Sprague-Dawley rats (250–300 g)	25 ng	Fourth ventricle, 10	o	Cerebral aqueduct was blocked with cold cream	Spadaro *et al.*, 1990
	Sprague-Dawley rats (250–300 g)	25 ng	Lateral ventricle, 10	o	There was a block within the third ventricle	Spadaro *et al.*, 1990
Footshock-induced freezing	Rats	100–300 ng	i.c.v., 24	—	Rats received footshocks of 0.79 mA, 1 sec each, 20 sec apart	Sherman *et al.*, 1987
	Sprague-Dawley rats	1 μg	i.c.v., 30	—		Abreu *et al.*, 1990
	Sprague-Dawley rats	1 μg	i.c.v., during 9 days (×1)	—		Abreu *et al.*, 1990

(*continued*)

TABLE 2. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
		Free observation	Sprague-Dawley rats (150–200 g)	10–20 μg/5 μL	i.c.v., 0	—	CRF increased grooming behavior in the home cage	Morley and Levine, 1982
			CD-1 mice (25–35 g)	1 μg/2 μL	i.c.v., 30	—	Motor movements appeared as bursts of activity followed by periods of immobility	Dunn and Berridge, 1987
		Gastric emptying	Rats	21–210 pmol/rat	Intracisternally, 5	—	Gastric emptying was inhibited	Hagiwara *et al.*, 1986
			Rats	61–600 pmol/rat	i.v., 5	—	Gastric emptying was inhibited	Hagiwara *et al.*, 1986
			Rats	210 pmol/rat	Lateral hypothalamus, 5	o		Hagiwara *et al.*, 1986
			Rats	210 pmol/rat	Paraventricular nucleus, 5	o		Hagiwara *et al.*, 1986
		Gastrointestinal motility	NMRI mice (20–30 g)	5 μg	i.c.v., 30	—	CRF produced gastrointestinal disturbances that were mimicked by acoustic and cold stress	Bueno and Gué, 1988
			NMRI mice (20–30 g)	5 μg	i.p., 30	o		Bueno and Gué, 1988
			Sprague-Dawley rats (250–300 g)	0.1–1 nmol/10 μL	i.c.v., 20	—	CRF decreased gastric emptying and small bowel transit, and increased large bowel transit	Lenz *et al.*, 1988a
		Geller-Seifter conflict test	Wistar rats (250–300 g)	1 μg/μL	i.c.v., 60	—		Britton *et al.*, 1985
			Wistar rats (200–250 g)	1 μg	i.c.v., 60	—		Britton, K. T. *et al.*, 1986b
			Wistar rats (200–250 g)	0.5 μg	i.c.v., 15	—	A continuous reinforcement schedule was used	Britton *et al.*, 1992
			Wistar rats (250 g)	0.5 μg/2 μL	i.c.v., 30	—		Thatcher Britton and Koob, 1986
			Rats	0.01–1 μg	i.c.v.	—		Thatcher Britton *et al.*, 1987
		Grooming	Rats	0.5–1 μg	i.c.v., 10–180	—	Grooming was increased	Britton *et al.*, 1984
			Hooded Lister rats	50, 200–250 pmol/2 μL	i.c.v., 15	—	Grooming was increased	Elkabir *et al.*, 1990
			Hooded Lister rats	50 pmol/0.5 μL	Amygdala, 5	—	Grooming was increased	Elkabir *et al.*, 1990
			Sprague-Dawley rats (275–300 g)	250–500 ng/0.5 μL	Nucleus accumbens shell, 0	—	Grooming was increased	Holahan *et al.*, 1997
			Sprague-Dawley rats (225–300 g)	0.3 μg/5 μL	i.c.v., 20	—	Grooming was increased	Sherman and Kalin, 1986
			Wistar rats (140–180 g)	0.3 μg/1 μL	i.c.v., 15	—	Grooming was increased	Veldhuis and De Wied, 1984
			Sprague-Dawley rats (180–200 g)	0.3–3 μg	i.c.v., 0	—	Grooming was increased under novel conditions	Sherman and Kalin, 1987
			Sprague-Dawley rats	1 μg	i.c.v., 30	—	Grooming was increased	Abreu *et al.*, 1990
			Sprague-Dawley rats (250–300 g)	0.8 μg/2 μL	i.c.v., 15	—	Grooming was increased in the home cage	Lazosky and Britton, 1991
			Sprague-Dawley rats (250–300 g)	0.5 μg/0.5 μL	Paraventricular nucleus, 0	—	Grooming was increased	Krahn *et al.*, 1988

	Rats	0.5–1 μg	i.v.	o		Britton *et al.*, 1984
	Sprague-Dawley rats (225–300 g)	0.3–3 μg/0.3 mL	s.c., 0	o		Sherman and Kalin, 1986
	Sprague-Dawley rats	1 μg	i.c.v., during 9 days (×1)	o		Abreu *et al.*, 1990
Hole-board	Wistar rats (200–250 g)	0.5–2 μg	i.c.v., 60	o	Rats were stressed with repeated handling and surgery	Adamec *et al.*, 1991
	Wistar rats (200–250 g)	0.5–2 μg	i.c.v., 60	o		Adamec *et al.*, 1991
Isolation-induced behavioral changes	Preweaning guinea-pigs	5 μg/5 μL	i.c.v. (freehand), 90	—	Vocalizing was decreased	Hennessy *et al.*, 1992
	Albino guinea-pig pups	7–14 μg	s.c., 60	—	Vocalization and locomotion were decreased, and crouch, eye-close, and pilo-erection were increased	Hennessy *et al.*, 1995
	Albino guinea-pig pups	7–14 μg	s.c., 60	—	Vocalization and locomotion were decreased	Hennessy *et al.*, 1991
	Preweaning guinea-pigs	14 μg	s.c., 60	?	Vocalizing and locomotor activity were decreased	Becker and Hennessy, 1993
	Preweaning guinea-pigs	5 μg/5 μL	i.c.v. (cannula), 90	o		Hennessy *et al.*, 1992
Light/dark test	C57/BL mice		i.c.v.	—		Guanowsky and Seymour, 1993
	C57/BL mice	0.32–3.2 μg	i.c.v.	—		Guanowsky *et al.*, 1997
Locomotor activity in home cage	Wistar rats (300–420 g)	1–10 μg/2 μL	i.c.v., 0	—	Locomotor activity was increased	Morimoto *et al.*, 1993
	Rats	0.5 μg	i.c.v., 0	—	Locomotor activity was increased	Britton, D. R. *et al.*, 1986
	Rats	0.8 μg	i.v., 0	o		Britton, D. R. *et al.*, 1986
Mental stress-induced colonic motor alterations	Sprague-Dawley rats (350–500 g)	0.1–1 μg/5 μL	i.c.v., 30	—	Rats received 6 series of electric footshocks (1.5 mA, 180 msec)	Gué *et al.*, 1991
Monkey behavior	Rhesus monkeys (4–6 kg)	20–180 μg	i.c.v., 0	—	The drug increased arousal and produced huddling	Kalin *et al.*, 1983
Monkeys in home cage	Rhesus monkeys	10–125 μg/200 μL	i.v.	—	The treatment produced a behavioral inhibition	Kalin, 1985
Multicompartment chamber	Mice	10–50 ng	i.c.v.	—	CRF produced a decrease in investigatory behavior similar to that observed after restraint stress	Berridge and Dunn, 1987b
Observation of gross behavioral change	Sprague-Dawley rats (250–275 g)	0.1–1 μg	i.c.v., 10	—	Grooming was increased	Jones *et al.*, 1997
Open-field	Wistar rats (200–230 g)	0.15 nmol/2 μL	i.c.v., 60	—		Sutton *et al.*, 1982
	Sprague-Dawley rats (300 g)	150 pmol/2 μL	i.c.v., 60	—		Britton *et al.*, 1982
	Sprague-Dawley rats (180–230 g)	0.01–1 μg/1 μL	Amygdala, 0	—	Decrease in locomotor activity, rearing, and hole poking	Liang and Lee, 1988
	BALB/c mice (20–25 g)	0.01 μg/0.4 μL	Dendate gyrus of hippocampus, 3 hr	—	There was an increase in locomotor activity in the center of the open-field	Lee and Tsai, 1989
	BALB/c mice (20–25 g)	0.02 μg/0.5 μL	Amygdala, 3 hr	—	There was an increase in locomotor activity in the center of the open-field	Lee and Tsai, 1989

(*continued*)

TABLE 2. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
			Sprague-Dawley rats (250 g)	60 pmol/2 μL	i.c.v., 30	—		Britton and Indyk, 1990
			Wistar rats (310–330 g)	0.1–0.4 μg/5 μL	i.c.v., 20	—		Kumar and Karanth, 1996
			BALB/c mice (20–25 g)	0.2 μg/2 μL	i.c.v., 3 hr	—	The drug increased center region activity	Lee *et al.*, 1987
			Wistar rats (200–300 g)	0.015–7.5 nmol/2 μL	s.c., 60	o		Sutton *et al.*, 1982
			BALB/c mice (20–25 g)	0.05 μg/0.7 μL	Caudate nucleus, 3 hr	o		Lee and Tsai, 1989
		Open-field drink test	Rats	25–500 ng/ cannula	Parabrachial nucleus, 0	—	Drinking in the lit area was reduced	Aaron *et al.*, 1991
			Sprague-Dawley rats	25–250 ng/ cannula	Locus coeruleus, 0	—	Drinking in the lit area was reduced	Weiss *et al.*, 1994
			Rats	250 ng/cannula	Dorsal tegmentum, 0	o		Aaron *et al.*, 1991
		Operant conflict paradigm	Rats	0.75 μg	i.c.v.	—		Britton *et al.*, 1997a
		Potentiated startle reflex	Sprague-Dawley rats	1 μg	i.c.v., 60–70	—	Animals were exposed to 120-dB acoustic startle stimuli	Schulz *et al.*, 1996
			Wistar rats (200–220 g)	1 μg/rat	i.c.v.	—		Swerdlow *et al.*, 1986
			Sprague-Dawley rats (280–340 g)	0.5–1 μg/5 μL	i.c.v., 20 min–6 hr	—		Liang *et al.*, 1992b
			Sprague-Dawley rats (280–340 g)	0.01–1 μg/5 μL	Intracisternal, 0	—		Liang *et al.*, 1992a
			Sprague-Dawley rats (280–340 g)	1 μg/5 μL	Intrathecal, 0	—	Small potentiation	Liang *et al.*, 1992a
			Sprague-Dawley rats (280–340 g)	0.01–0.3 μg/5 μL	Amygdala, 0	o		Liang *et al.*, 1992a
		Punished lever pressing test	Rats	0.1–5.6 μg	i.c.v.	—	A multiple FR schedule was used	Aulisi *et al.*, 1989
		Rat pup isolation calls	Sprague-Dawley rats (5–6 days old)	0.01–0.1 μg/1 μL	i.c.v., 0	?	Vocalizing was decreased	Insel and Harbaugh, 1989
			Sprague-Dawley rats (5–6 days old)	1–10 μg/100 μL	s.c., 30	o		Insel and Harbaugh, 1989
		Separation-induced distress vocalizations	Chicks (4 days old)	1 μg	i.c.v.	—	Animals were exposed to a plain box	Panksepp *et al.*, 1988
			Chicks (4 days old)	1 μg	i.c.v.	—	Animals were exposed to a mirrored box	Panksepp *et al.*, 1988
			Chicks (4 days old)	0.2–5 μg	i.c.v.	—	Animals were exposed to a plain box	Panksepp *et al.*, 1988
			Chicks (4 days old)	0.2–5 μg	i.c.v.	—	Animals were exposed to a plain box	Panksepp *et al.*, 1988
		Shock-induced freezing	Sprague-Dawley rats (180–200 g)	300 ng	i.c.v., 22–25	—	Rats received 3 1-sec footshocks (0.79 mA) at 20-sec intervals	Sherman and Kalin, 1988
		Social interaction test	Hooded Lister rats (250 g)	0.1–0.3 μg/4 μL	i.c.v., 20	—	Light intensity was 30 lux	Dunn and File, 1987
			Rats	100 ng	i.c.v.	—		File *et al.*, 1988
					i.c.v.	—		Rohrbach *et al.*, 1996

		Stimulus-induced increase in arousal	Squirrel monkeys (800–1200 g)	0.1–10 μg/10 μL	i.c.v., 5	—		Winslow *et al.*, 1989
		Stress-induced fighting	Wistar rats (180–200 g)	0.01–0.1 μg/2 μL	i.c.v., 30	—	Pairs of rats were exposed to inescapable footshocks (0.3–0.5 mA)	Tazi *et al.*, 1987
		Stress-induced gastrointestinal alterations	Sprague-Dawley rats (200–250 g)	0.1–1 μg/5 μL	i.c.v., 30	—	Rats were subjected to partial body restraint	Lenz *et al.*, 1988b
CRF antibodies		Elevated plus-maze after social defeat stress	Rats		Paraventricular nucleus	+		Menzaghi *et al.*, 1992
CRF antiserum	Decreased CRF level	Elevated plus-maze	Wistar rats (180–220 g)		i.c.v., for 14 days	o		Sarnyai *et al.*, 1995
			Wistar rats (200–250 g)		i.c.v., 24 hr	o		Bíró *et al.*, 1993
CRF antiserum + CCK_8 (1 μg)		Elevated plus-maze	Wistar rats (200–250 g)		i.c.v., 24 hr	(+)		Bíró *et al.*, 1993
CRF antiserum + cocaine withdrawal		Elevated plus-maze	Wistar rats (180–220 g)		i.c.v., for 14 days	(+)	Antagonism of the anxiogenic effects of cocaine withdrawal	Sarnyai *et al.*, 1995
CRF + 8-OH-DPAT (5-HT_{1A} agonist, 0.25–0.5 mg/kg)	Endogenous peptide	Grooming	Sprague-Dawley rats (250–300 g)	0.8 μg/2 μL	i.c.v., 15	(+)		Lazosky and Britton, 1991
CRF + α-helical $CRF_{9–41}$		Light/dark test	C57/BL mice		i.c.v.	(+)		Guanowsky and Seymour, 1993
		Social interaction test			i.c.v.	(+)		Rohrbach *et al.*, 1996
CRF + α-helical $CRF_{9–41}$ (0.5 μg/0.5 μL)		Elevated plus-maze	Wistar rats (200–250 g)		DPAG, 10	(+)		Martins *et al.*, 1997
CRF + α-helical $CRF_{9–41}$ (1 μg/1 μL)		Rat pup isolation calls	Sprague-Dawley rats (5–6 days old)	0.01 μg	i.c.v., 0	(+)		Insel and Harbaugh, 1989
CRF + α-helical $CRF_{9–41}$ (1–25 μg/μl)		Acoustic startle reflex	Wistar rats (200–220 g)	1 μg/2 μL	i.c.v., 5	(+)	Rats were presented with 5 118-dB white noise bursts	Swerdlow *et al.*, 1989
CRF + α-helical $CRF_{9–41}$ (10 μg/10 μL)		Stimulus-induced increase in arousal	Squirrel monkeys (800–1200 g)	10 μg	i.c.v., 5	(+)		Winslow *et al.*, 1989
CRF + α-helical $CRF_{9–41}$ (10 μg/5 μL)		Stress-induced gastrointestinal alterations	Sprague-Dawley rats (200–250 g)	1 nmol	i.c.v., 45	(+)	Rats were subjected to partial body restraint	Lenz *et al.*, 1988b
CRF + α-helical $CRF_{9–41}$ (10 nmol)		Stress-induced gastrointestinal alterations	Sprague-Dawley rats (200–250 g)	1 nmol	i.v., 45	—	(1) No antagonism of the effects of CRF on colonic motility (2) Rats were subjected to partial body restraint	Lenz *et al.*, 1988b
CRF + α-helical $CRF_{9–41}$ (25–50 μg/5 μL)		Potentiated startle reflex	Sprague-Dawley rats (280–340 g)		i.c.v., 5 prior or 90 after CRF	(+)		Liang *et al.*, 1992b
CRF + α-helical $CRF_{9–41}$ (3–6 μg/5 μL)		Acoustic startle reflex	Sprague-Dawley rats (350–430 g)		Bed nucleus of the stria terminalis, 0	(+)	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997b

(*continued*)

TABLE 2. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
CRF + α-helical CRF_{9-41} (5 μg/5 μL)		Mental stress-induced colonic motor alterations	Sprague-Dawley rats (350–500 g)	0.5 μg	i.c.v., 40	(+)		Gué *et al.*, 1991
		Open-field	Wistar rats (310–330 g)	0.1–0.4 μg	i.c.v., 30	(+)		Kumar and Karanth, 1996
CRF + α-helical CRF_{9-41} (50 μg)		Conflict test	Sprague-Dawley rats (276–300 g)	1 μg/3 μL	i.c.v., 5	(+)	Rats were trained under an FR20 schedule	de Boer *et al.*, 1992
		Elevated plus-maze	Wistar rats (200–250 g)	2 μg	i.c.v., 60	(+)		Adamec *et al.*, 1991
		Elevated plus-maze	Rats	2 μg	i.c.v.	(+)		McKay and Adamec, 1993
		Isolation-induced behavioral changes	Albino guinea-pig pups	7 μg	s.c., 60	(+)	Antagonism of the effects of CRF on behavior (e.g., decrease in vocalizing, increase in crouch)	Hennessy *et al.*, 1995
CRF + α-helical CRF_{9-41} (50 μg/3 μL)		Hypophysectomy + elevated plus-maze	Wistar rats (140–180 g)	2 μg	i.c.v., 60	(+)		Adamec and McKay, 1993
CRF + α-helical CRF_{9-41} (50 μg/5 μL)		Food intake	Sprague-Dawley rats (300–350 g)		i.c.v., 60	(+)	Animals were subjected to immobilization stress	Krahn *et al.*, 1986
CRF + α-helical CRF_{9-41} (50–200 μg)		Geller-Seifter conflict test	Wistar rats (200–250 g)		i.c.v., 30	(+)		Britton, K. T. *et al.*, 1986b
CRF + adrenalectomy		Gastric emptying	Rats	210 pmol/rat	Intracisternally, 5	—	No antagonism of the effects of CRF on gastric emptying	Hagiwara *et al.*, 1986
		Gastrointestinal transit	Sprague-Dawley rats (250–300 g)	1 nmol/10 μL	i.c.v., 20	—	No antagonism of the effects of CRF on gastrointestinal transit	Lenz *et al.*, 1988a
CRF + alcohol (0.75 mg/kg)		Geller-Seifter conflict test	Wistar rats (250 g)	0.5 μg/2 μL	i.c.v., 30	(+)		Thatcher Britton and Koob, 1986
CRF + amygdala chemical lesion		Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	—	(1) No antagonism of the behavioral effects of CRF (2) Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997b
CRF + amygdala lesion		Acoustic startle reflex	Rats		i.c.v.	—	Lesion did not block the anxiogenic-like effects of CRF	Lee and Davis, 1995
		Potentiated startle reflex	Sprague-Dawley rats (280–340 g)	1 μg/5 μL	i.c.v., 0	(+)		Liang *et al.*, 1992a
		Potentiated startle reflex	Sprague-Dawley rats (280–340 g)	1 μg/5 μL	Intrathecal, 0	—	No antagonism	Liang *et al.*, 1992a
CRF + anterior commissure electrolytic lesion		Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	—	(1) No antagonism of the behavioral effects of CRF (2) Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997a
CRF + atenolol (100 μg, β_1 antagonist)		Defensive withdrawal	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	(+)		Yang and Dunn, 1990
CRF + atropine (1 mg/kg)		Colonic function	Sprague-Dawley rats (290–370 g)	0.6 nmol/100 nL	Paraventricular nucleus, 60	(+)	Antagonism of the effects of CRF on colonic motor response	Mönnikes *et al.*, 1992a
CRF + bed nucleus of the stria terminalis chemical lesion		Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	(+)	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997b

CRF + bed nucleus of the stria terminalis lesion	Acoustic startle reflex	Rats		i.c.v.	(+)	Lesion blocked the anxiogenic-like effects of CRF	Lee and Davis, 1995
CRF + buspirone (5-HT_{1A} agonist, 2–4 mg/kg)	Grooming	Sprague-Dawley rats (250–300 g)	0.8 μg/2 μL	i.c.v., 15	(+)		Lazosky and Britton, 1991
CRF + CGP 12177 (1 mg/kg, peripheral β antagonist)	Defensive withdrawal	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	—	No anatagonism of the anxiogenic effects of CRF	Yang and Dunn, 1990
CRF + CGP 20712A (10 μg, β_1 antagonist)	Defensive withdrawal	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	(+)		Yang and Dunn, 1990
CRF + chlordiazepoxide	Geller-Seifter conflict test	Wistar rats (250–300 g)	0.5 μg/2 μL	i.c.v., 60	(+)		Britton, *et al.*, 1985
	Potentiated startle reflex	Wistar rats (200–220 g)	1 μg/rat	i.c.v.	(+)		Swerdlow *et al.*, 1986
	Social interaction test	Hooded Lister rats (250 g)	0.1 μg/4 μL	i.c.v., 20	(+)	Light intensity was 30 lux	Dunn and File, 1987
	Social interaction test			i.c.v.	(+)		Rohrbach *et al.*, 1996
CRF + chlordiazepoxide (10 μg)	Conflict test	Sprague-Dawley rats (276–300 g)	1 μg/3 μL	i.c.v., 5	(+)	Rats were trained under an FR20 schedule	de Boer *et al.*, 1992
CRF + chlordiazepoxide (2.5 mg/kg)	Acoustic startle reflex	Rats	1 μg	i.c.v.	(+)		Swerdlow *et al.*, 1985
CRF + chlordiazepoxide (3–10 mg/kg)	Conflict test	White Carneau pigeons (1 year old)	30 μg/5 μL	i.c.v., 60	(+)	A multiple FR schedule was used	Zhang and Barrett, 1990
CRF + chlordiazepoxide (5 mg/kg)	Defensive withdrawal	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	(+)		Yang *et al.*, 1990
	Geller-Seifter conflict test	Rats	0.01–1 μg	i.c.v.	(+)		Thatcher Britton *et al.*, 1987
CRF + chlordiazepoxide (5–10 mg/kg)	Conditioned suppression of reponding	Wistar rats (200–250 g)	0.5–1 μg/2 μL	i.c.v., 60	(+)		Britton *et al.*, 1988
CRF + clonidine (0.025 mg/kg)	Defensive withdrawal	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	(+)		Yang *et al.*, 1990
CRF + CP-154,526 (0.32–3.2 μg)	Light/dark test	C57/BL mice		i.c.v.	(+)		Guanowsky *et al.*, 1997
CRF + CP-154,526 (17.8 mg/kg)	Potentiated startle reflex	Sprague-Dawley rats		i.c.v.	(+)	Animals were exposed to 120-dB acoustic startle stimuli	Schulz *et al.*, 1996
CRF + CRF antiserum (5 μg)	Gastrointestinal motility	NMRI mice (20–30 g)	5 μg	i.c.v.	(+)		Bueno and Gué, 1988
CRF + $CRF_{1–20}$ (10 nmol)	Stress-induced gastrointestinal alterations	Sprague-Dawley rats (200–250 g)	1 nmol	i.c.v., 45	—	(1) No antagonism of the effects of CRF on colonic motility (2) Rats were subjected to partial body restraint	Lenz *et al.*, 1988b
CRF + D-Phe $CRF_{12–41}$ (3.2 μg)	Potentiated startle reflex	Sprague-Dawley rats		i.c.v., 80	(+)	Animals were exposed to 120-dB acoustic startle stimuli	Schulz *et al.*, 1996

(*continued*)

TABLE 2. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
CRF + *d*-propranolol (2.5–10 mg/kg)		Conditioned suppression of responding	Rats (160–180 g)	0.5 μg/1 μL	i.c.v., 30	—		Cole and Koob, 1988
CRF + dexamethasone		Geller-Seifter conflict test	Wistar rats (250–350 g)	0.5–1 μg	i.c.v., 60	—		Britton, K. T. *et al.*, 1986a
CRF + dexamethasone (100 mg/kg)		Grooming	Rats	0.5–1 μg	i.c.v., 10–180	—	(1) Grooming was increased (2) Effect not altered by pituitary-adrenal system blockade	Britton, *et al.*, 1984
		Locomotor activity in home cage	Rats	0.5 μg	i.c.v., 0	—	Effect not altered by pituitary-adrenal system blockade	Britton, D. R. *et al.*, 1986
CRF + diazepam (0.5 mg/kg)		Mental stress-induced colonic motor alterations	Sprague-Dawley rats (350–500 g)	0.5 μg/5 μL	i.c.v., 30	—	Diazepam did not antagonize the effects of CRF on colonic motility	Gué *et al.*, 1991
CRF + diazepam (2 mg/kg)		Open-field	BALB/c mice (20–25 g)	0.2 μg/2 μL	i.c.v., 3 hr	(+)		Lee *et al.*, 1987
CRF + *dl*-propranolol (5 mg/kg)		Defensive withdrawal	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	(+)		Yang *et al.*, 1990
CRF + dorsal hippocampus electrolytic lesion		Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	—	(1) No antagonism of the behavioral effects of CRF (2) Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997a
CRF + FG 7142 (10–20 mg/kg)		Conditioned suppression of reponding	Wistar rats (200–250 g)	0.5–1 μg/2 μL	i.c.v., 60	—	Potentiation of the anxiogenic effects of CRF	Britton *et al.*, 1988
CRF + fimbria transection		Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	(+)	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997a
CRF + flumazenil (10 μg)		Conflict test	Sprague-Dawley rats (276–300 g)	1 μg/3 μL	i.c.v., 5	(+)	Rats were trained under an FR20 schedule	de Boer *et al.*, 1992
CRF + flumazenil (3 mg/kg)		Elevated plus-maze	Sprague-Dawley rats	0.5 μg/5 μL	i.c.v., 20	—	No antagonism of the anxiogenic effects of CRF	Moy *et al.*, 1997
CRF + flumazenil (4 mg/kg)		Elevated plus-maze	Rats	100 ng	i.c.v.	—	Flumazenil did not block the anxiogenic-like effects of CRF	File *et al.*, 1988
		Social interaction test	Rats	100 ng	i.c.v.	—	Flumazenil did not block the anxiogenic-like effects of CRF	File *et al.*, 1988
CRF + flumazenil (6–12 mg/kg)		Conditioned suppression of responding	Wistar rats (200–250 g)	0.5–1 μg/2 μL	i.c.v., 60	(+)	Antagonism of the anxiogenic effects of CRF	Britton *et al.*, 1988
CRF + ganglionic blockade (250–300 g)		Gastrointestinal transit	Sprague-Dawley rats	1 nmol/ 10 μL	i.c.v., 20	(+)	Antagonism of the effects of CRF on gastric emptying and small bowel transit	Lenz *et al.*, 1988a
CRF + hypophysectomy		Elevated plus-maze	Rats	2 μg	i.c.v.	—	Anxiogenic-like effects not altered by hypophysectomy	McKay and Adamec, 1993
		Elevated plus-maze	Wistar rats (140–180 g)	2 μg/3 μL	i.c.v., 60	—		Adamec and McKay, 1993
		Exploratory chamber	CD-1 mice (24–28 g)	50 ng/4 μL	i.c.v., 10	—		Berridge and Dunn, 1989
		Free observation	Sprague-Dawley rats (150–200 g)	20 μg/5 μL	i.c.v., 0	—	Increase in grooming not altered by hypophysectomy	Morley and Levine, 1982
		Gastrointestinal transit	Sprague-Dawley rats (250–300 g)	1 nmol/10 μL	i.c.v., 20	—	No antagonism of the effects of CRF on gastrointestinal transit	Lenz *et al.*, 1988a

	Mental stress-induced colonic motor alterations	Sprague-Dawley rats (350–500 g)	0.5 μg/5 μL	i.c.v., 30	—	Hypophysectomy did not antagonize the effects of CRF on colonic motility	Gué *et al.*, 1991
CRF + ICI 118551 (0.5 mg/kg, peripheral β_2 antagonist)	Defensive withdrawal	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	—	No antagonism of the anxiogenic effects of CRF	Yang and Dunn, 1990
CRF + *l*-propranolol (2.5 mg/kg, β antagonist)	Defensive withdrawal	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	(+)		Yang and Dunn, 1990
CRF + *l*-propranolol (2.5–10 mg/kg)	Conditioned suppression of responding	Rats (160–180 g)	0.5 μg/1 μL	i.c.v., 30	(+)		Cole and Koob, 1988
CRF + lateral septum electrolytic lesion	Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	—	(1) No antagonism of the behavioral effects of CRF (2) Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997a
CRF + medial septum chemical lesion	Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	—	(1) No antagonism of the behavioral effects of CRF (2) Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997a
CRF + medial septum electrolytic lesion	Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	(+)	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997a
CRF + naloxone (1–5 m/kg)	Isolation-induced behavioral changes	Albino guinea-pig pups	7–14 μg	s.c., 60	—	No antagonism of the behavioral effects of CRF	Hennessy *et al.*, 1991
CRF + naloxone (1.25 mg/kg)	Exploratory behavior	CD-1 mice (25–35 g)	75 ng/4 μL	i.c.v., 10	(+)	Apparatus was a multicompartment chamber	Berridge and Dunn, 1986
CRF + NE blockade	Gastrointestinal transit	Sprague-Dawley rats (250–300 g)	1 nmol/10 μL	i.c.v., 20	(+)	Antagonism of the effects of CRF on gastric emptying and small bowel transit	Lenz *et al.*, 1988a
CRF + opioid blockade	Gastric emptying	Rats	210 pmol/rat	Intracisternally, 5	—	No antagonism of the effects of CRF on gastric emptying	Hagiwara *et al.*, 1986
	Gastrointestinal transit	Sprague-Dawley rats (250–300 g)	1 nmol/ 10 μL	i.c.v., 20	(+)	Antagonism of the effects of CRF on gastric emptying and small bowel transit	Lenz *et al.*, 1988a
CRF + paraventricular nucleus lesion	Potentiated startle reflex	Sprague-Dawley rats (280–340 g)	1 μg/5 μL	i.c.v., 0	—	No antagonism	Liang *et al.*, 1992a
CRF + prazosin (0.1 mg/kg)	Defensive withdrawal	Sprague-Dawley rats (250–300 g)	50 ng	i.c.v., 25	(+)		Yang *et al.*, 1990
CRF + SC241	Social interaction test			i.c.v.	(+)		Rohrbach *et al.*, 1996
CRF + vagotomy	Colonic function	Sprague-Dawley rats (290–370 g)	0.6 nmol/100 nL	Paraventricular nucleus, 60	—	No antagonism of the effects of CRF on colonic motor response	Mönnikes *et al.*, 1992a
CRF + vagotomy	Gastrointestinal transit	Sprague-Dawley rats (250–300 g)	1 nmol/10 μL	i.c.v., 20	—	No antagonism of the effects of CRF on gastrointestinal transit	Lenz *et al.*, 1988a
CRF + vasopressin (10 pmol)	Grooming	Hooded Lister rats	50 pmol/0.5 μL	Amygdala, 5	—	Self-grooming was increased synergistically	Elkabir *et al.*, 1990
CRF + vasopressin (100 pmol)	Grooming	Hooded Lister rats	50–200 pmol/ 2 μL	i.c.v., 15	—	Self-grooming was increased synergistically	Elkabir *et al.*, 1990

(*continued*)

TABLE 2. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
CRF + ventral hippocampus chemical lesion		Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	—	(1) No antagonism of the behavioral effects of CRF (2) Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997b
CRF + whole septum electrolytic lesion		Acoustic startle reflex	Sprague-Dawley rats (350–430 g)	1 μg/5 μL	i.c.v., 0	(+)	Rats received 60 startle stimuli of 105 dB	Lee and Davis, 1997a
CRF + YY941		Social interaction test			i.c.v.	(+)		Rohrbach *et al.*, 1996
$CRF_{1–20}$	Inactive N-terminal fragment	Stress-induced gastrointestinal alterations	Sprague-Dawley rats (200–250 g)	10 nmol	i.c.v., 15	o	Rats were subjected to partial body restraint	Lenz *et al.*, 1988b
$CRF_{6–33}$	CRF-binding protein	Elevated plus-maze	Rats	25–125 μg	i.c.v., 15	o		Behan *et al.*, 1995
SC241	CRF_1 antagonist	Social interaction test				+		Rohrbach *et al.*, 1996
Transgenic mice	CRF overproduction	Elevated plus-maze	CRH-Tg^+			—	Animals showed a marked reduction in open arm activity compared with control animals	Stenzel-Poore *et al.*, 1996
	CRF_1 knockout	Exploration tests				+		Koob and Gold, 1997
	CRF overproduction	Exploration tests				—		Koob and Gold, 1997
		Open-field	CRH-Tg^+			—	Animals showed a marked reduction in locomotor activity compared with control animals	Stenzel-Poore *et al.*, 1996
	CRF inhibition					o	No behavioral differences were observed between mutant and wild-type mice	Miczek, 1997
Urocortin	Endogenous CRF_2 ligand	Elevated plus-maze	Wistar rats (220–250 g)	0.1 nmol/5 μL	i.c.v., 30	—		Moreau *et al.*, 1997
			Sprague-Dawley rats (250–275 g)	0.1–1 μg	i.c.v., 30	—		Jones *et al.*, 1997
			Wistar rats	0.01–10 mg/2 μL	i.c.v., 5	o		Spina *et al.*, 1996
		Light/dark test	BALB/c mice (10 weeks)	0.02–0.06 nmol	i.c.v., 30	—		Moreau *et al.*, 1997
		Observation of gross behavioral change	Sprague-Dawley rats (250–275 g)	0.1–1 μg	i.c.v., 10	—	Grooming was increased	Jones *et al.*, 1997
		Open-field	BALB/c mice (10 weeks)	0.06 nmol	i.c.v., 30	—		Moreau *et al.*, 1997
Urocortin + α-helical $CRF_{9–41}$ (2.6–8 nmol)		Open-field	BALB/c mice (10 weeks)	0.06 nmol	i.c.v., 30	(+)		Moreau *et al.*, 1997

Urocortin + diazepam (0.1–1)		Open-field	BALB/c mice (10 weeks)	0.06 nmol	i.c.v., 30	(+)	Moreau *et al.*, 1997
Urotensin	Endogenous CRF_2 ligand	Elevated plus-maze	Wistar rats	10 μg/2 μL	i.c.v., 5	— Weak effects	Spina *et al.*, 1996
YY941	CRF_1 antagonist	Social interaction test				+	Rohrbach *et al.*, 1996

[1]+, anxiolysis; o, inactive; —, anxiogenesis; (+), antagonism of anxiogenic-like effects; (−), antagonism of anxiolytic-like effects.
DPAG, dorsal periaqueductal gray; FR, fixed ratio; i.c.v., intracerebroventricular; ODN, oligonucleotide; VI, variable interval.

primary target involved in the mediation of the anxiogenic-like effects of CRF.

2.2.3. Behavioral effects of corticotropin-releasing factor receptor antagonists in animal models of anxiety and stress. Several peptide and nonpeptide CRF receptor antagonists have been studied extensively in experimental models of anxiety (Table 2). For example, central application of the CRF fragment and competitive CRF receptor antagonist α-helical $CRF_{9–41}$ was reported to reduce anxiety-related responses in rodents in the elevated plus-maze, hole-board, potentiated startle, Geller-Seifter conflict, and conditioned emotional response tests (see Fig. 5). Moreover, α-helical $CRF_{9–41}$ was found to prevent behavioral (i.e., defensive withdrawal, decrease in exploratory behavior, freezing) and physiological (i.e., colonic transit, increase in paradoxical sleep) changes following exposure to stressors such as restraint, inescapable footshocks, social defeat, or immersion in cold water. However, negative results have also been reported with this compound in the acoustic startle, elevated plus-maze, Geller-Seifter conflict, and open-field tests. In addition, the drug failed to block freezing behavior and gastrointestinal disturbances produced by the application of footshocks or restraint. Furthermore, α-helical $CRF_{9–41}$ may exert anxiogenic-like effects in the elevated plus-maze test in rats and may increase arousal in squirrel monkeys. Although the reasons for these inconsistencies are not fully understood, at least some of the negative results may be due to the use of limited dose ranges. In addition, it was suggested that α-helical $CRF_{9–41}$ may produce anxiogenic-like activity in nonstressed animals when the endogenous tone of CRF is apparently low and may produce anxiolytic-like effects in stressed animals when CRF levels are increased (Menzaghi *et al.*, 1994). To illustrate this idea, two studies have shown that α-helical $CRF_{9–41}$ produced anxiolytic-like effects in the elevated plus-maze only after animals had been stressed by exposure to conspecific aggression (Heinrichs *et al.*, 1992; Menzaghi *et al.*, 1994). Moreover, findings from Adamec and colleagues (1991) have revealed that repeated handling altered the anxiolytic-like effects of α-helical $CRF_{9–41}$ in the elevated plus-maze. In line with these results is the report of Conti *et al.* (1994), who showed that α-helical $CRF_{9–41}$ was more efficacious and more potent in BALB/c mice, which are described as "emotional" animals, than in three "nonemotional" strains (i.e., NIH Swiss, CF-1, CD) in the elevated plus-maze.

Studies with other CRF receptor antagonists further support the hypothesis that baseline levels of stress are of crucial importance when investigating the behavioral actions of such compounds. For instance, the peripheral administration of the nonpeptide CRF antagonist CP-154,526 produced anxiolytic-like effects in the rat elevated plus-maze only when mean baseline levels of exploration of the aversive parts of the apparatus were low (Lundkvist *et al.*, 1996; Griebel *et al.*, 1998). Similarly, in BALB/c mice, CP-154,526 was found to reduce anxiety-related responses in

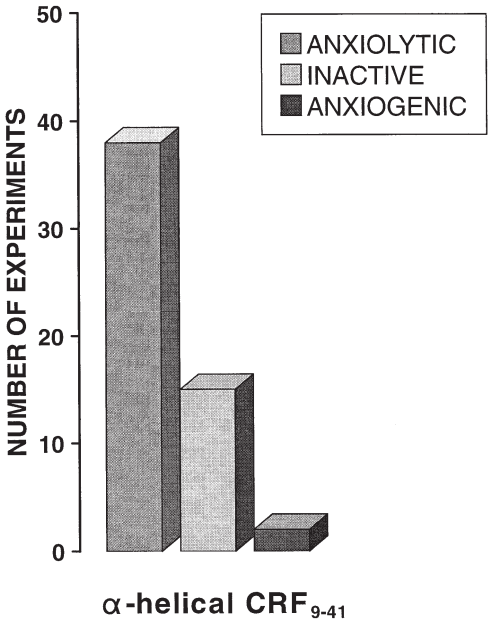

FIGURE 5. Illustration of the outcome of the peptide receptor antagonists α-helical $CRF_{9–41}$ in animal models of anxiety.

the light/dark test, but only weakly affected these behaviors in a free-exploration test, which represents a less stressful situation than the former (Griebel *et al.*, 1998). Moreover, CP-154,526 reduced defensive behaviors of isolated Swiss mice confronted with a rat, a situation that appears to be particularly stressful for animals since they have no possibility to escape from the test apparatus and confrontation with the threat stimulus is unavoidable (Griebel *et al.*, 1998).

2.2.4. Corticotropin-releasing factor and human studies. Although there is no direct evidence that CRF or CRF receptor ligands may modulate anxiety in humans, clinical data suggesting a role for CRF in anxiety disorders have been accumulating over recent years. Thus, cerebrospinal fluid (CSF) levels of CRF have been shown to be elevated in patients suffering from OCD (Altemus *et al.*, 1994), post-traumatic stress disorder (Stout *et al.*, 1995), but not panic disorder (Jolkkonen *et al.*, 1993). However, in the last case, a blunted effect of intravenously administered CRF on ACTH levels has been reported (Roy Byrne *et al.*, 1986). Similarly, hypersecretion of CRF in the brain may be involved in OCD, since a blunted ACTH response to intravenously administered CRF in OCD patients has been observed (Servant, 1997).

In conclusion, the last few years have seen important advances in the understanding of CRF and its mechanisms of action in modulating responses to stress. Particularly, the findings that CRF stimulation increases anxiety-related behaviors in a variety of animal models suggest that agents acting at CRF receptors may have therapeutic effects in anxiety- or stress-related disorders. The development of nonpeptide and lipophilic CRF receptor antagonists as novel anxiolytics is being actively pursued by a number of major pharmaceutical companies, and data on the therapeutic potential of these compounds should become available soon.

2.3. *Neuropeptide Y*

NPY is a 36 amino acid peptide of the pancreatic polypeptide (PP) family that includes PP and peptide YY (PYY) (Tatemoto *et al.*, 1982). It is one of the most abundant peptides within the body (Hunt *et al.*, 1981; Allen *et al.*, 1984; Dawbarn *et al.*, 1984; Gray and Morley, 1986). Binding studies with NPY fragments or analogues and the related peptides PYY and PP have permitted the identification of at least three NPY receptor types classified as Y_1–Y_3 (Wahlestedt and Reis, 1993). While the Y_1 and the Y_2 receptors are members of the seven-transmembrane G-protein-coupled superfamily of receptors, the characterization of the Y_3 receptor has not been completed (Herzog *et al.*, 1992; Larhammar *et al.*, 1992; Rose *et al.*, 1995). NPY is widely distributed throughout the peripheral nervous system and the CNS. In the periphery, NPY is found both in peripheral nerves and in the circulation, where it is an important co-transmitter with NE (Pernow *et al.*, 1989; Lundberg *et al.*, 1990). In the brain, significant NPY levels are found in most brain regions, including cerebral cortex, hippocampus, thalamus, and brainstem (Gray and Morley, 1986). While the Y_3 receptor has been identified only in the brainstem (Wahlestedt and Reis, 1993), high densities of Y_1 and Y_2 receptors have been described in a variety of brain regions. Y_1 receptors are predominant in the cerebral cortex, thalamus, and certain nuclei of the amygdala, whereas Y_2 receptors are found mainly in the hippocampus, substantia nigra-lateralis, hypothalamus, and brainstem (Dumont *et al.*, 1995). The presence of NPY and NPY receptors in brain regions known to be activated in stress (e.g., amygdala, hypothalamus) has provided the rationale for studying NPY and related peptides in animal models of anxiety.

2.3.1. Behavioral effects of central application of neuropeptide Y in animal models of anxiety. A number of studies in rats have shown that intracerebroventricular injection of NPY or PYY produces a behavioral profile that is consistent with an anxiolytic-like action (Table 3). Importantly, these effects were observed in a variety of anxiety models, including the elevated plus-maze test (Heilig *et al.*, 1989; Broqua *et al.*, 1994, 1995; Heilig, 1995; Kirby *et al.*, 1995), the Vogel (Heilig *et al.*, 1989) and Geller-Seifter (Heilig *et al.*, 1992, 1993; Britton *et al.*, 1997b) conflict procedures, and the fear-potentiated startle test (Wettstein *et al.*, 1994; Broqua *et al.*, 1995). Moreover, in the study of Britton and colleagues, NPY and PYY produced anxiolytic-like activity comparable with that observed with the reference anxiolytic chlordiazepoxide. The findings that the anti-conflict effects of NPY were completely reversed by the α_2-adrenergic receptor antagonist idazoxan (Heilig *et al.*, 1989), but not altered by the BZ receptor antagonist flumazenil, and only partially blocked by the GABA recep-

tor ligand isopropylbicyclophosphate (Britton *et al.*, 1997b), suggest that NE, but not the GABA/BZ receptor complex, may be involved in the anti-anxiety effects of NPY. This idea is consistent with the co-localization of NPY with NE cell bodies in many brain regions.

2.3.2. Behavioral effects of neuropeptide Y fragments and neuropeptide Y receptor ligands in animal models of anxiety. A series of studies have shown that intracerebroventricular infusion of high-affinity Y_1 agonists, including [Gly^6, Glu^{26}, Lys^{29}, Pro^{34}]-NPY, [Leu^{31}, Pro^{34}]-NPY, but not [Cys^{7,21}, Pro^{34}]-NPY, yielded anxiolytic-like activity in the Geller-Seifter conflict test (Heilig *et al.*, 1993; Britton *et al.*, 1997b), the elevated plus-maze (Broqua *et al.*, 1994, 1995), and/or the fear-potentiated startle procedure in rats (Wettstein *et al.*, 1994; Broqua *et al.*, 1995). The reasons that may account for the negative findings with [Cys^{7,21}, Pro^{34}]-NPY are unclear. It has been suggested that the compound may act on a yet uncharacterized subclass of Y_1 receptors in the brain (Kirby *et al.*, 1995). Alternatively, it was speculated that the path of degradation or elimination of this peptide in the brain (i.e., an alteration of the cystine crossbridge) may yield a less effective Y_1 binder (Kirby *et al.*, 1995). Recently, a highly selective nonpeptide Y_1 receptor antagonist, BIBP3226, was found to produce anxiogenic-like effects in the elevated plus-maze in rats (Kask *et al.*, 1996, 1997), thereby confirming the involvement of Y_1 receptors in the modulation of anxiety-related behaviors.

Unlike Y_1 receptor agonists, NPY analogues that bind selectively to Y_2 receptors, such as [Glu^{2,32}, d-Ala^6, d-Dpr^{27}, Lys^{28}]-NPY or the C-terminal fragment of NPY $NPY_{13–36}$, generally have been found to be inactive in anxiety models (Heilig *et al.*, 1989; Broqua *et al.*, 1994, 1995; Wettstein *et al.*, 1994; Britton *et al.*, 1997b). One study revealed positive effects of $NPY_{13–36}$ in the Geller-Seifter conflict test (Heilig *et al.*, 1993). However, in this study, $NPY_{13–36}$ produced only a marginally significant increase of punished responding. Together, these results suggest that the anxiolytic-like effects of NPY may be mediated primarily by activation of Y_1 receptors. This idea is further supported by the finding that antisense inhibition of Y_1 receptor expression itself produced anxiogenic-like effects (Wahlestedt *et al.*, 1993) and blocked the anxiolytic-like action of bilateral NPY administration in the amygdala (Heilig, 1995).

2.3.3. Clinical evidence for the involvement of neuropeptide Y in anxiety disorders. There are a few studies that showed that NPY might be involved in human anxiety. For example, Widerlöv *et al.* (1988) found that the lowest CSF NPY concentrations among depressed patients were in those individuals with the most severe anxiety symptoms. Furthermore, Boulenger *et al.* (1996) observed higher plasma NPY-like immunoreactivity in patients with panic disorder as compared with healthy volunteers. However, these findings are at variance with those of Stein and co-workers (1996). These authors reported that basal and stress-stimulated plasma levels of NPY in patients with panic disorder and social phobia did not differ from levels in healthy volunteers. The reasons underlying these discrepancies are unknown, but underscore the need for further study in this area.

In conclusion, the robust anxiolytic-like effects observed with Y_1 receptor agonists in a variety of anxiety models suggest that these compounds may have the potential to become an alternative to BZs for the treatment of anxiety disorders. However, to date, only synthetic peptide NPY agonists have been developed and, as mentioned in Section 2.2, the usefulness of peptides as therapeutic agents is limited. Future search for selective nonpeptide Y_1 receptor agonists hopefully will provide new drugs for the treatment of anxiety disorders.

2.4. *Tachykinins*

The mammalian TKs are a group of neuropeptides that includes SP, NK-A, and NK-B. The biological actions of TKs are mediated via the activation of three G-protein-coupled seven-transmembrane domain receptors designated as NK_1, NK_2, and NK_3 (Regoli *et al.*, 1994). Both NK_1 and NK_3 receptors are widely distributed in the CNS, while the NK_2 receptor is found mainly in smooth muscle of the gastrointestinal, respiratory, and urinary tracts, with considerably lower levels located in the CNS (Otsuka and Yoshioka, 1993; Maggi, 1995). Brain areas traditionally implicated in the control of fear and anxiety, such as the hypothalamus, amygdala, hippocampus, and periaqueductal gray matter, all express significant densities of TK NK receptors (for a review, see Otsuka and Yoshioka, 1993).

2.4.1. Behavioral effects of substance P, neurokinin A, and neurokinin B analogs in animal models of anxiety. The behavioral effects of the preferential NK_1 receptor agonist SP have been investigated in several studies using the elevated plus-maze and the social interaction tests (Table 4). The administration of picomolar concentrations of SP into the lateral ventricles, the region of the nucleus basalis magnocellularis, the bed nucleus of stria terminalis, or the basolateral nucleus of the amygdala produced anxiogenic-like effects in the elevated plus-maze (De Lima and Ribeiro, 1996; Jentiens *et al.*, 1996; Teixeira *et al.*, 1996). However, anxiolytic-like effects were observed in the social interaction test after the application of 1 ng of SP in the nucleus basalis magnocellularis (Hasenöhrl *et al.*, 1996; Jentiens *et al.*, 1996). Moreover, the intraperitoneal administration of 50 μg/kg of SP produced anxiolytic-like effects in the elevated plus-maze, while the 500 μg/kg dose was anxiogenic (Hasenöhrl *et al.*, 1996; Jentiens *et al.*, 1996). Although these findings provide evidence for a role for SP in anxiety, it is important to note that the effects of SP in anxiety models may be dependent on dose and specific brain region.

While the central administration of the preferential NK_2 receptor agonist NK-A and/or the selective NK_2 receptor agonist [β-Ala^8]NK-A-(4–10), a fragment of NK-A, has

TABLE 3. Effects of Drugs Modulating the NPY System in Animal Models of Anxiety

Drugs	Mechanisms	Models	Animals	Doses	Routes of administration, latency (min)	Effects[1]	Comments	References
[Cys^{7,21}, Pro^{34}]-NPY	Y_1 agonist	Elevated plus-maze	Rats	3 nmol/5 μL	i.c.v., 60	o		Kirby *et al.*, 1995
		Geller-Seifter conflict test	Wistar rats (200–250 g)	2.5–15 μg/rat	i.c.v., 15	o		Britton *et al.*, 1997b
[Glu^{2,32}, d-Ala^{6}, d-Dpr^{27},Lys^{28}]-NPY	Y_2 agonist	Geller-Seifter conflict test	Wistar rats (200–250 g)	2.5–15 μg/rat	i.c.v., 15	o		Britton *et al.*, 1997b
[Gly^{6}, Glu^{26}, Lys^{29}, Pro^{34}]-NPY	Y_1 agonist	Geller-Seifter conflict test	Wistar rats (200–250 g)	10–15 μg/rat	i.c.v., 15	+		Britton *et al.*, 1997b
[Leu^{31}, Pro^{34}]-NPY	Y_1 agonist	Elevated plus-maze	Sprague-Dawley rats (220–240 g)	0.7–7 nmol/ 5 μL	i.c.v., 60	+		Broqua *et al.*, 1995
			Rats	0.7–7 nmol	i.c.v., 60	+		Broqua *et al.*, 1994
			ddY mice (7 weeks)	70 pmol/4 μL	i.c.v., 10	+		Nakajima *et al.*, 1998
		Fear-potentiated startle	Long-Evans rats (220–240 g)	2.3–13.2 nmol/ 5 μL	i.c.v., 60	+		Broqua *et al.*, 1995
			Rats	2.3–13.2 nmol	i.c.v., 60	+		Wettstein *et al.*, 1994
		Geller-Seifter conflict test	Wistar rats (200–275 g)	50–100 pmol/ 0.5 μL	Amygdala, 15	+		Heilig *et al.*, 1993
			Wistar rats (200–250 g)	5–15 μg/rat	i.c.v., 15	+		Britton *et al.*, 1997b
Antisense ODN	Y_1 inhibition	Elevated plus-maze	Wistar rats (250 g)	50 μg	i.c.v., 3 days (×2)	—		Heilig, 1995
			Rats	50 μg	i.c.v., 2 days (×2)	—		Wahlestedt *et al.*, 1993
BIBP3226	Y_1 antagonist	Elevated plus-maze	Wistar rats (270–350 g)	0.5–5 μg	i.c.v., 20	—		Kask *et al.*, 1996
			Wistar rats (330–380 g)	5 μg/5 μL	i.c.v., 60	—		Kask *et al.*, 1997
BIBP3226 + diazepam (0.5 mg/kg)		Elevated plus-maze	Wistar rats (270–350 g)	5 μg	i.c.v., 20	(+)		Kask *et al.*, 1996
			ddY mice (7 weeks)	7 pmol/4 μL	i.c.v., 10	—		Nakajima *et al.*, 1998
			ddY mice (7 weeks)	7 pmol or 0.7 nmol/4 μL	i.c.v., 10	−/+	Biphasic effects	Nakajima *et al.*, 1998
		Fear-potentiated startle	Long-Evans rats (220–240 g)	0.023–2.3 nmol/5 μL	i.c.v., 60	+		Broqua *et al.*, 1995
			Rats	0.23–2.3 nmol	i.c.v., 60	+		Wettstein *et al.*, 1994
		Geller-Seifter conflict test	Wistar rats (200–275 g)	1–5 nmol/5 μL	i.c.v., 60	+		Heilig *et al.*, 1993
			Wistar rats (200–275 g)	50–100 pmol/ 0.5 μL	Amygdala, 15	+		Heilig *et al.*, 1993
			Wistar rats (200–275 g)	1–5 nmol	i.c.v., 60	+		Heilig *et al.*, 1992
			Wistar rats (200–250 g)	4–6 μg/rat	i.c.v., 15	+		Britton *et al.*, 1997b
		Open-field	Sprague-Dawley rats (220–250 g)	1–4 nmol/5 μL	i.c.v., 60	?	NPY decreased spontaneous activity, suggesting sedation	Heilig and Murison, 1987b
		Stress-induced gastric erosion	Sprague-Dawley rats (220–250 g)	2 nmol/5 μL	i.c.v., 60	+	Animals were exposed to water-immersion stress	Heilig and Murison, 1987a
		Vogel conflict test	Sprague-Dawley rats (250–270 g)	0.2–5 nmol/5 μL	i.c.v., 60	+	Water deprivation of 24 hr and electric shocks of 0.16 mA/ 2 sec	Heilig *et al.*, 1989
Neuropeptide Y + CRF (0.75 μg)		Operant conflict paradigm	Rats	1 μg	i.c.v.	(+)		Britton *et al.*, 1997a
Neuropeptide Y + flumazenil (3–12 mg/kg)		Conflict test	Wistar rats (200–250 g)	16 μg/rat	i.c.v., 15	+	No antagonism of the anxiolytic-like effects of NPY	Britton *et al.*, 1997b

Neuropeptide Y + idazoxan (α_2 antagonist)		Vogel conflict test	Sprague-Dawley rats (250–270 g)	0.2–5 nmol/ 5 μL	i.c.v., 60	(–)		Heilig *et al.*, 1989
Neuropeptide Y + IPPO (picrotoxin ligand, 5–15 mg/kg)		Conflict test	Wistar rats (200–250 g)	16 μg/rat	i.c.v., 15	+	No antagonism of the anxiolytic-like effects of NPY	Brittoin *et al.*, 1997b
NPY + Y_1 antisense ODN		Elevated plus-maze	Wistar rats (250 g)	100 pmol/side	Amygdala, 15	(–)		Heilig, 1995
$NPY_{13–36}$	Y_2 agonist	Elevated plus-maze	ddY mice (7 weeks)	20 pmol/4 μL	i.c.v., 10	—		Nakajima *et al.*, 1998
			Sprague-Dawley rats (220–240 g)	0.7–7 nmol/ 5 μL	i.c.v., 60	o		Broqua *et al.*, 1995
			Sprague-Dawley rats (250–270 g)	0.42–2 nmol/ 5 μL	i.c.v., 60	o		Heilig *et al.*, 1989
			Rats	0.7–7 nmol	i.c.v., 60	o		Broqua *et al.*, 1994
		Fear-potentiated startle	Long-Evans rats (220–240 g)	2.3–13.2 nmol/ 0.5 μL	i.c.v., 60	o		Broqua *et al.*, 1995
			Rats	Up to 13.2 nmol	i.c.v., 60	o		Wettstein *et al.*, 1994
		Geller-Seifter conflict test	Wistar rats (200–275 g)	100–200 pmol/ 0.5 μL	Amygdala, 15	+	Weak effects	Heilig *et al.*, 1993
			Wistar rats (200–250 g)	2.5–15 μg/rat	i.c.v., 15	o		Britton *et al.*, 1997b
		Vogel conflict test	Sprague-Dawley rats (250–270 g)	0.4–2 nmol/ 0.5 μL	i.c.v., 60	o	Water deprivation of 24 hr and electric shocks of 0.16 mA/ 2 sec	Heilig *et al.*, 1989
$NPY_{2–36}$	$Y_{1/2}$ agonist	Elevated plus-maze	Sprague-Dawley rats (220–240 g)	0.07–2.3 nmol/ 5 μL	i.c.v., 60	+		Broqua *et al.*, 1995
		Elevated plus-maze	Rats	0.07–2.3 nmol	i.c.v., 60	+		Broqua *et al.*, 1994
		Fear-potentiated startle	Long-Evans rats (220–240 g)	0.023–2.3 nmol/5 μL	i.c.v., 60	+		Broqua *et al.*, 1995
			Rats	0.23–2.3 nmol	i.c.v., 60	+		Wettstein *et al.*, 1994
Pancreatic peptide	Endogenous peptide	Geller-Seifter conflict test	Wistar rats (200–250 g)	5–15 μg/rat	i.c.v., 15	o		Britton *et al.*, 1997b
Peptide YY	Endogenous peptide	Elevated plus-maze	Sprague-Dawley rats (220–240 g)	0.07–2.3 nmol/ 5 μL	i.c.v., 60	+		Broqua *et al.*, 1995
		Elevated plus-maze	Rats	0.07–2.3 nmol	i.c.v., 60	+		Broqua *et al.*, 1994
		Fear-potentiated startle	Long-Evans rats (220–240 g)	0.023–2.3 nmol/5 μL	i.c.v., 60	+		Broqua *et al.*, 1995
			Rats	0.23–2.3 nmol	i.c.v., 60	+		Wettstein *et al.*, 1994
		Geller-Seifter conflict test	Wistar rats (200–250 g)	10–15 μg/rat	i.c.v., 15	+		Britton *et al.*, 1997b

[1]+, anxiolysis; o, inactive; —, anxiogenesis; (+), antagonism of anxiogenic-like effects; (–), antagonism of anxiolytic-like effects.
i.c.v., intracerebroventricular; IPPO, isopropylbicyclophosphate.

TABLE 4. Effects of Drugs Modulating Tachykinin System in Animal Models of Anxiety

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
[β-Ala^8] Neurokinin A-(4-10)	NK_2 agonist	Elevated plus-maze	Swiss mice (25–30 g)	1000 pmol/5 μL	i.c.v., 0	—		Teixeira *et al.*, 1996
			Mice	500 pmol/5 μL	i.c.v., 5	—	Animals were placed in an open-field 5 min prior to testing	De Lima *et al.*, 1995
CGP 49823	NK_1 antagonist	Elevated plus-maze	Rats		p.o.	o		Vassout *et al.*, 1994
		Social interaction test	Hooded Lister rats (200–230 g)	3–30	p.o., 90	+	Animals were tested in an unfamiliar arena	File, 1997
			Hooded Lister rats (200–230 g)	10	p.o., for 3 weeks (×1)	+	Animals were tested in an unfamiliar arena	File, 1997
			Hooded Lister rats (200–230 g)	10	p.o., for 6 weeks (×1)	+	Animals were tested in an unfamiliar arena	File, 1997
			Rats	MED = 10	p.o.	+		Vassout *et al.*, 1994
			Rats	MED = 10	p.o., subchronic	+		Vassout *et al.*, 1994
CP-96,345	NK_1 antagonist	Light/dark	Swiss mice (17–37 g)	5	i.p.	+	Nonspecific effects	Zernig *et al.*, 1993
			Swiss mice	1–10	i.p., 45	+	Nonspecific effects	Zernig *et al.*, 1992
CP-96,345 + naloxone (2 mg/kg)		Light/dark	Swiss mice	5	i.p., 45	+	Nonspecific effects	Zernig *et al.*, 1992
FK 888	NK_1 antagonist	Elevated plus-maze	Swiss mice (25–30 g)	1 and 100 pmol/ 5 μL	i.c.v., 0	+		Teixeira *et al.*, 1996
			Mice	0.1–500 pmol/ 5 μL	i.c.v., 5	+	Animals were placed in an open-field 5 min prior to testing	De Lima *et al.*, 1995
			Wistar rats	100 pmol	i.c.v., 5	o		De Lima and Ribeiro, 1996
GR 64349	NK_2 agonist	Open-field	Rats	100–1000 pmol	Dorsal raphé	—		Stratton *et al.*, 1993a
		Social interaction test	Rats	10–300 pmol	Dorsal raphé	—	Low light familiar conditions	Stratton *et al.*, 1993a
GR100679	NK_2 antagonist	Elevated plus-maze	Rats	3–300 pmol	Dorsal raphé	+	High light unfamiliar conditions	Stratton *et al.*, 1993
		Light/dark	CRH mice (28–35 g)	0.02–200 μg	s.c., 30	+		Stratton *et al.*, 1993b
GR115211	NK_2 antagonist	Social interaction test	Rats	3–300 pmol	Dorsal raphé	+	High light unfamiliar conditions	Stratton *et al.*, 1993a
GR159897	NK_2 antagonist	Elevated plus-maze	Rat	1.25–125 ng	Dorsal raphé	+		Stratton *et al.*, 1994
		Human intruder response test	Male and female marmosets (259–400 g)	0.2, 10–50 μg	s.c., 30	+		Walsh *et al.*, 1995
		Light/dark	Mice	0.0005–50 μg	s.c., 30	+		Stratton *et al.*, 1994
			CRH mice (28–35 g)	0.0005, 0.05–50 μg	s.c., 30	+		Walsh *et al.*, 1995
		Social interaction test	Rat	1.25–125 ng	Dorsal raphé	+		Stratton *et al.*, 1994
Neurokinin A	Preferential NK_2 agonist	Elevated plus-maze	Swiss mice (25–30 g)	10–100 pmol/ 5 μL	i.c.v., 0	—		Teixeira *et al.*, 1996
RP 67580	NK_1 antagonist	Light/dark	Swiss mice (17–37 g)	0.03–10	i.p.	o		Zernig *et al.*, 1993
Senktide	NK_3 agonist	Elevated plus-maze	Mice	0.1–500 pmol/ 5 μL	i.c.v., 5	+	Animals were placed in an open-field 5 min prior to testing	De Lima *et al.*, 1995

SR 140333	NK_1 antagonist	Light/dark	Swiss mice		i.p., 30	o	60-W white light	Bernatzky and Saria, 1995
SR 48968	NK_2 antagonist	Elevated plus-maze	Swiss mice (25–30 g)	1–100 pmol/ 5 μL	i.c.v., 0	+		Teixeira *et al.*, 1996
			Mice	0.1–500 pmol/ 5 μL	i.c.v., 5	+	Animals were placed in an open-field 5 min prior to testing	De Lima *et al.*, 1995
		Human intruder response test	Male and female marmosets (259–400 g)	10–50 μg	s.c., 30	+		Walsh *et al.*, 1995
		Light/dark	Swiss mice		i.p., 30	+	60-W white light	Bernatzky and Saria, 1995
			CRH mice (28–35 g)	0.0005–5 μg	s.c., 30	+		Walsh *et al.*, 1995
			CRH mice (28–35 g)	0.05–5 μg	s.c., 30	+		Stratton *et al.*, 1993b
SP	Preferential NK_1 agonist	Elevated plus-maze	Rats	50 μg	i.p.	+		Jentiens *et al.*, 1996
			Rats	1 ng	Nucleus basalis magnocellularis	+		Jentiens *et al.*, 1996
			Rat	50 μg	i.p.	+		Hasenöhrl *et al.*, 1996
			Rat	1 ng	Nucleus basalis magnocellularis	+		Hasenöhrl *et al.*, 1996
			Swiss mice (25–30 g)	1–10 pmol/5 μL	i.c.v., 0	—		Teixeira *et al.*, 1996
			Rats	0.5	i.p.	—		Jentiens *et al.*, 1996
			Swiss mice	10 pmol/2 μL	i.c.v., 5	—		De Lima *et al.*, 1997
			Rat	500 μg	i.p.	—		Hasenöhrl *et al.*, 1996
			Wistar rats	10 pmol	i.c.v., 5	—		De Lima and Ribeiro, 1996
			Wistar rats	10 pmol	Bed nucleus of the stria terminalis, 5	—		De Lima and Ribeiro, 1996
			Wistar rats	10 pmol	Basolateral nucleus of the amygdala, 5	—		De Lima and Ribeiro, 1996
			Mice	0.1–500 pmol/ 5 μL	i.c.v., 5	o	Animals were placed in an open-field 5 min prior to testing	De Lima *et al.*, 1995
		Social interaction test	Rats	1 ng	Nucleus basalis magnocellularis	+		Jentiens *et al.*, 1996
			Rat	1 ng	Nucleus basalis magnocellularis	+		Hasenöhrl *et al.*, 1996
SP methyl ester	NK_1 agonist	Elevated plus-maze	Swiss mice (25–30 g)	1–10 pmol/5 μL	i.c.v., 0	—		Teixeira *et al.*, 1996
			Mice	0.1–500 pmol/ 5 μL	i.c.v., 5	—	Animals were placed in an open-field 5 min prior to testing	De Lima *et al.*, 1995
			Wistar rats	10 pmol	i.c.v., 5	—		De Lima and Ribeiro, 1996
SP + *N*-*N*-nitro-L-arginine (0.02 μmol)	Preferential NK_1 agonist	Elevated plus-maze	Swiss mice	10 pmol/2 μL	i.c.v., 5	(+)		De Lima *et al.*, 1997

[1]+, anxiolysis; o, inactive; —, anxiogenesis; (+), antagonism of anxiogenic-like effects.
i.c.v., intracerebroventricular; MED, minimal effective dose.

been reported to produce anxiogenic-like effects in the murine elevated plus-maze (De Lima *et al.*, 1995; Teixeira *et al.*, 1996), studies on the action of the NK_3 receptor agonist NK-B are still lacking. However, the intracerebroventricular application of the NK-B analog senktide was found to induce anxiolytic-like activity in the elevated plus-maze in mice (De Lima *et al.*, 1995), suggesting that the central TK NK_3 receptor may also play a modulatory role in anxiety.

2.4.2. Behavioral effects of nonpeptide neurokinin receptor antagonists in animal models of anxiety. Recently, several classes of nonpeptide antagonists at NK_1 and NK_2 receptors have been identified (Mills, 1997). Studies using a range of NK_1 receptor antagonists have indicated that these compounds display anxiolytic-like activity in exploration models and in social interaction procedures (Table 4). For example, CGP 49823 has been reported to have anxiolytic-like effects in the rat social interaction test (Vassout *et al.*, 1994; File, 1997) and to increase social investigation in gerbils (Cutler, 1994). However, the picture is less clear with other selective NK_1 receptor antagonists such as FK 888. Although the drug produced anxiolytic-like activity in the mouse elevated plus-maze (De Lima *et al.*, 1995; Teixeira *et al.*, 1996), these effects were not confirmed in a subsequent experiment in rats (De Lima and Ribeiro, 1996). The reasons for these differences are unclear, but it is important to note that in the two studies where FK 888 was found active, significant effects were observed at nonconsecutive doses and only on one index of anxiety (i.e., open arm time), thereby suggesting weak anxiolytic-like activity. In contrast, studies on the effects of selective NK_2 receptor antagonists in anxiety models have invariably reported that these compounds display anti-anxiety activity. The most studied drugs in this group are GR159897 (Beresford *et al.*, 1995) and SR 48968 (Edmonds-Alt *et al.*, 1992). In rodents, anxiolytic-like effects have been reported for both compounds in the light/dark exploration, social interaction, and elevated plus-maze procedures (Stratton *et al.*, 1993b, 1994; Bernatzky and Saria, 1995; De Lima *et al.*, 1995; Walsh *et al.*, 1995; Teixeira *et al.*, 1996). Moreover, GR159897 and SR 48968 significantly increased the time spent by marmosets at the front of the cage following confrontation with a human "threat," an effect that is consistent with an anxiolytic-like action (Walsh *et al.*, 1995). Interestingly, the magnitude of the anxiolytic-like effects of GR159897 and SR 48968 was generally similar to that produced by the classical anti-anxiety agents diazepam or chlordiazepoxide, but unlike these latter, the NK_2 receptor antagonists did not produce behavioral suppression at higher doses. In fact, GR159897 and SR 48968 produced positive effects over a wide dose range, with minimum dose levels in the microgram range.

In summary, the above data suggest that SP may play a physiological role in the modulation of anxiety and that this peptide is released by aversive environmental stimuli. However, the findings that NK_1 receptor ligands have variable and sometimes contradictory effects in anxiety models clearly demand further investigation. Although the anxiolytic-like effects of NK_2 receptor antagonists are compelling, it is important to note that these effects have been obtained only in exploration tests and social investigation procedures. Clearly, additional work with conflict tests needs to be done in order to compare further the anxiety-reducing potential of NK_2 receptor antagonists with that of classical anxiolytics.

2.5. *Natriuretic Peptides*

The NP system consists of the atrial (ANP), brain (BNP), and C-type (CNP) NPs. NPs act as natriuretic hormones in the periphery and play a role in the regulation of the homeostasis of body fluid, electrolytic balance, and blood pressure in the CNS (Nicholls, 1994), where specific NP-binding sites have been identified (Imura *et al.*, 1992). Polymerase chain reaction and *in situ* hybridization analysis demonstrated that NP mRNAs are co-expressed in the periventricular and paraventricular hypothalamic nuclei, indicating an involvement in the regulation of the adrenocortical and neurohypophyseal axes (Herman *et al.*, 1993). Consistent with this idea is the finding that intravenous injection of ANP inhibits the CRF-stimulated secretion of ACTH and cortisol in humans (Kellner *et al.*, 1992). NP receptors have also been found in the septum, the locus coeruleus, and the central nucleus of the amygdala, brain areas that are supposed to be involved in the modulation of emotional processes (Skofitsch *et al.*, 1985; Bianchi *et al.*, 1986).

2.5.1. Behavioral effects of natriuretic peptides in animal models of anxiety. Intracerebroventricular administration of ANP, BNP, and CNP was found to increase exploratory activity in the elevated plus-maze test in rats (Bíró *et al.*, 1995, 1996; Bhattacharya *et al.*, 1996a), and ANP displayed anxiolytic-like effects in the open-field test, the social interaction procedure, and in a model based on food consumption in a novel environment (Bhattacharya *et al.*, 1996a) (see Table 5). In contrast, ANP failed to alter punished responding in the Geller-Seifter conflict test in rats (Heilig *et al.*, 1992). This discrepancy cannot be attributed to differences in rat strains (Wistar rats were used in both studies) or to administration route and pretreatment (similar in all studies). However, the use of different experimental procedures may account for this variability, since there is now growing evidence that different animal models of anxiolytic activity actually may be measuring different facets of anxiety (Rodgers, 1997; Ramos and Mormede, 1998).

In an attempt to understand the mechanisms underlying the anxiolytic-like activity of NPs in the elevated plus-maze, a few studies have examined a possible interaction between these peptides and several neurotransmitter systems. Results showed that the anti-anxiety action of ANP and CNP was prevented by haloperidol, phenoxybenzamine, and propranolol, but not by atropine, bicuculline, methysergide, and naloxone (Bíró *et al.*, 1995, 1996; Bhattacharya *et al.*, 1996a). In addition, the effects of ANP in

TABLE 5. Effects of Drugs Modulating NP System in Animal Models of Anxiety

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
ANP	Neuropeptide	Elevated plus-maze	Wistar rats (200–250 g)	100–200 ng/ 2 μL	i.c.v., 30	+		Bíró *et al.*, 1995
			Wistar rats (180–200 g)	200–500 ng/ 5 μL	i.c.v., 0	+		Bhattacharya *et al.*, 1996a
		Geller-Seifter conflict test	Wistar rats (200–275 g)	1.5–6 nmol	i.c.v., 30	o		Heilig *et al.*, 1992
		Novelty-induced feeding suppression	Wistar rats (180–200 g)	200–500 ng/ 5 μL	i.c.v., 0	+		Bhattacharya *et al.*, 1996a
		Open-field	Wistar rats (180–200 g)	200–500 ng/ 5 μL	i.c.v., 0	+		Bhattacharya *et al.*, 1996a
		Social interaction test	Wistar rats (180–200 g)	200–500 ng/ 5 μL	i.c.v., 0	+		Bhattacharya *et al.*, 1996a
ANP + atropine (2 mg/kg)		Elevated plus-maze	Wistar rats (200–250 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1995
ANP + bicuculline (1 mg/kg)		Elevated plus-maze	Wistar rats (200–250 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1995
ANP + flumazenil (5 mg/kg)		Elevated plus-maze	Wistar rats (180–200 g)	200–500 ng/ 5 μL	i.c.v., 0	+	No antagonism of the anxiolytic-like effects	Bhattacharya *et al.*, 1996a
ANP + haloperidol (0.01 mg/kg)		Elevated plus-maze	Wistar rats (200–250 g)	200 ng/2 μL	i.c.v., 30	(–)		Bíró *et al.*, 1995
ANP + isatin (10 mg/kg)		Elevated plus-maze	Wistar rats (180–200 g)	200–500 ng/ 5 μL	i.c.v., 0	(–)		Bhattacharya *et al.*, 1996a
ANP + methysergide (5 mg/kg)		Elevated plus-maze	Wistar rats (200–250 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1995
ANP + naloxone (0.1 mg/kg)		Elevated plus-maze	Wistar rats (200–250 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1995
ANP + phenoxybenzamine (2 mg/kg)		Elevated plus-maze	Wistar rats (200–250 g)	200 ng/2 μL	i.c.v., 30	(–)		Bíró *et al.*, 1995
ANP + propranolol (10 mg/kg)		Elevated plus-maze	Wistar rats (200–250 g)	200 ng/2 μL	i.c.v., 30	(–)		Bíró *et al.*, 1995
Atriopeptin II	Residue peptide	Elevated plus-maze	Wistar rats (260 g)	0.05	i.p., 20	+	Animals were socially defeated	Strohle *et al.*, 1997
			Wistar rats (260 g)	2.5–5 μg/5 μL	i.c.v., 10	+	Animals were socially defeated	Strohle *et al.*, 1997
			Wistar rats (260 g)	0.25 μg/0.5 μL	Amygdala, 5	+	Animals were socially defeated	Strohle *et al.*, 1997
		Open-field	Wistar rats (220–260 g)	5–10 μg/rat	i.c.v., 20	+		Poggioli *et al.*, 1992
BNP	Neuropeptide	Elevated plus-maze	Wistar rats (180–220 g)	100–200 ng/ 2 μL	i.c.v., 30	+		Bíró *et al.*, 1996
BNP + atropine (2 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	(–)		Bíró *et al.*, 1996
BNP + bicuculline (1 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1996
BNP + haloperidol (0.01 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1996
BNP + methysergide (5 mg/kg)		Elevated plus-maze	Wistar rats (180–200 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1996

(*continued*)

TABLE 5. Continued

Drugs	Mechanisms	Models	Animals	Doses (mg/kg)	Routes of administration, latency (min)	Effects[1]	Comments	References
BNP + naloxone (0.1 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1996
BNP + phenoxybenzamine (2 mg/kg)		Elevated plus-maze	Wistar rats (180–200 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1996
BNP + propranolol (10 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	(–)		Bíró *et al.*, 1996
CNP	Neuropeptide	Elevated plus-maze	Wistar rats (180–220 g)	100–200 ng/ 2 μL	i.c.v., 30	+		Bíró *et al.*, 1996
CNP + atropine (2 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1996
CNP + bicuculline (1 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1996
CNP + haloperidol (0.01 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	(–)		Bíró *et al.*, 1996
CNP + methysergide (5 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1996
CNP + naloxone (0.1 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	+	No antagonism of the anxiolytic-like effects	Bíró *et al.*, 1996
CNP + phenoxybenzamine (2 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	(–)		Bíró *et al.*, 1996
CNP + propranolol (10 mg/kg)		Elevated plus-maze	Wistar rats (180–220 g)	200 ng/2 μL	i.c.v., 30	(–)		Bíró *et al.*, 1996
Isatin	ANP receptor antagonist	Elevated plus-maze	Wistar mice (25–30 g)	20	i.p., 45	—		Bhattacharya and Acharya, 1993
			Wistar mice (25–30 g)	15	i.p., 15	—		Bhattacharya *et al.*, 1991
			Wistar rats (180–200 g)	15	i.p., 30	—		Bhattacharya *et al.*, 1996b
			Wistar rats (180–200 g)	10	i.p., 30	o		Bhattacharya *et al.*, 1996a
		Open-field	Wistar mice (25–30 g)	20	i.p., 15	—		Bhattacharya *et al.*, 1991
		Social behavior	Rhesus monkeys (*Macaca mulatta*)	20	i.m., 0	—		Palit *et al.*, 1997
		Social interaction test	Charles Foster rats (150–180 g)	20	i.p., 15	—		Bhattacharya *et al.*, 1991
Isatin + (–)-propranolol (5 mg/kg)		Elevated plus-maze	Wistar mice (25–30 g)	20	i.p., 45	—	No interaction	Bhattacharya and Acharya, 1993
Isatin + 5,6-DHT (25 μg/mouse)		Elevated plus-maze	Wistar mice (25–30 g)	20	i.p., 45	(–)		Bhattacharya and Acharya, 1993
Isatin + 5-MeODMT (2 mg/kg)		Elevated plus-maze	Wistar mice (25–30 g)	10	i.p., 45	o	No interaction	Bhattacharya and Acharya, 1993
Isatin + buspirone (5 mg/kg)		Elevated plus-maze	Wistar mice (25–30 g)	20	i.p., 45	—	No interaction	Bhattacharya and Acharya, 1993
Isatin + flumazenil (10 mg/kg)		Elevated plus-maze	Wistar mice (25–30 g)	20	i.p., 45	—	No interaction	Bhattacharya and Acharya, 1993

Isatin + fluoxetine (10 mg/kg)	Elevated plus-maze	Wistar mice (25–30 g)	10	i.p., 45	—	Fluoxetine potentiated the anxiogenic-like effects	Bhattacharya and Acharya, 1993
Isatin + ketanserin (5 mg/kg)	Elevated plus-maze	Wistar mice (25–30 g)	20	i.p., 45	—	No interaction	Bhattacharya and Acharya, 1993
Isatin + metergoline (5 mg/kg)	Elevated plus-maze	Wistar mice (25–30 g)	20	i.p., 45	(–)		Bhattacharya and Acharya, 1993
Isatin + pimozide (2 mg/kg)	Elevated plus-maze	Wistar mice (25–30 g)	20	i.p., 45	(–)		Bhattacharya and Acharya, 1993
Isatin + quipazine (5 mg/kg)	Elevated plus-maze	Wistar mice (25–30 g)	10	i.p., 45	—	Quipazine potentiated the anxiogenic-like effects	Bhattacharya and Acharya, 1993
Isatin + zacopride (5 mg/kg)	Elevated plus-maze	Wistar mice (25–30 g)	20	i.p., 45	(–)		Bhattacharya and Acharya, 1993

[1] +, anxiolysis; o, inactive; —, anxiogenesis; (–), antagonism of anxiolytic-like effects.
5,6-DHT, 5,6-dihydroxytryptamine; i.c.v., intracerebroventricular; MeODMT, 5-methoxy-N,N-dimethyltryptamine.

the elevated plus-maze were unaffected by flumazenil (Bhattacharya *et al.*, 1996a). These findings suggest that the anxiolytic-like action of ANP and CNP presumably involve dopaminergic, α-, and/or β-adrenergic neurotransmission, and that there is little likelihood that these effects involve the GABA/BZ, 5-HT, cholinergic, and opiate systems. However, interaction experiments with BNP yielded somewhat different results. Thus, the anxiolytic-like activity of BNP was antagonized by pretreatment with atropine and propranolol, whereas phenoxybenzamine, haloperidol, bicuculline, methysergide, and naloxone did not prevent these effects (Bíró *et al.*, 1996). These differences between ANP and BNP are surprising as they share substantial amino acid sequence homology and have similar potency in their natriuretic, diuretic, vasorelaxant, and behavioral (i.e., they produced delayed extinction or response in the active and passive avoidance tests, respectively) effects (Bidzseranova *et al.*, 1992; Lang *et al.*, 1992). Direct comparisons between ANP and BNP have indicated that their cardiovascular, renal, and behavioral effects are indistinguishable from each other (Bidzseranova *et al.*, 1992; Lang *et al.*, 1992; Wigle *et al.*, 1992). Clearly, further studies are warranted in order to have a more complete understanding of the mechanisms underlying the anxiolytic-like effects of NPs.

2.5.2. Behavioral effects of natriuretic peptide receptor ligands in animal models of anxiety. The effects of central and peripheral administration of atriopeptin II, a 23 amino acid residue peptide of ANP (Ser^{103}–Arg^{125}), was investigated in the elevated plus-maze test in rats previously exposed to social defeat stress. Results showed that the intracerebroventricular, intra-amygdala, and intraperitoneal administration of atriopeptin II produced anxiolytic-like effects without affecting spontaneous locomotor activity (Strohle *et al.*, 1997). Furthermore, atriopeptin II was found to increase the number of crossings and rearings in the open-field test (Poggioli *et al.*, 1992), an effect that is consistent with reduced emotionality (Denenberg, 1969). Together, these results support further the anti-anxiety potential of NP.

Isatin (2,3-dioxoindole) has been identified as one of the constituents of tribulin, an endogenously occurring monoamine oxidase inhibitor, which has been postulated to function as an endocoid factor in stress and anxiety (Sandler *et al.*, 1988; Glover *et al.*, 1991). Receptor binding experiments have shown that isatin has little effect on a wide range of neurotransmitter (e.g., 5-HT, GABA, dopamine, adenosine), regulatory neuropeptide, and hormonal (e.g., CCK, NPY, SP, vasopressin, bombesin) receptors, but acts as an inhibitor of ANP binding (Glover *et al.*, 1995). In addition, the characteristic distribution of isatin in tissues, including the brain, with highest levels in the hippocampus, suggests that the compound may have a specific physiological role (Watkins *et al.*, 1990). Peripheral administration of isatin was found to decrease exploratory activity of rats and mice exposed to the elevated plus-maze

and to the open-field tests in the absence of significant action on spontaneous locomotor activity, thereby suggesting that the compound displayed specific anxiogenic-like effects (Bhattacharya *et al.*, 1991, 1996b; Bhattacharya and Acharya, 1993). In contrast, in another study, isatin failed to modify significantly the behavior of rats in the elevated plus-maze (Bhattacharya *et al.*, 1996a). However, this difference is readily explained by the fact that in the latter study, the authors used only a subanxiogenic dose (i.e., 10 mg/kg) of isatin. Moreover, in socially isolated rhesus monkeys (*Macaca mulatta*) removed from a familiar environment and restrained artificially, isatin produced a range of behavioral changes that were proposed to be somewhat similar to those seen in clinical anxiety (Palit *et al.*, 1997). For example, the compound decreased approach behavior, body contacts, and increased aggressiveness, vigilance, vocalization, and respiratory rate. Finally, isatin reduced the time spent in social investigation by paired rats in the social interaction test, an effect that was mimicked by the anxiogenic agent and α_2-adrenoceptor antagonist yohimbine. The likely mechanisms involved in the anxiogenic-like effects of isatin have been investigated in two studies. Bhattacharya and colleagues (1996a) showed that isatin antagonized the anxiolytic-like effects of ANP, thereby confirming its interaction with ANP binding sites. The same authors demonstrated in another study that pretreatment with the nonselective 5-HT receptor antagonist metergoline, the selective 5-HT_3 receptor antagonist zacopride, the 5-HT neurotoxin 5,6-DHT, and the mixed D_1/D_2 dopamine antagonist pimozide, but not propranolol, flumazenil, and the 5-HT_{1A} receptor partial agonist buspirone, attenuated the effects of isatin in the elevated plus-maze test. In addition, the anxiogenic-like action of a sub-effective dose (i.e., 10 mg/kg) of isatin was potentiated by the 5-HT reuptake inhibitor fluoxetine and to a lesser extent by the nonselective 5-HT_2 receptor agonist quipazine (Bhattacharya and Acharya, 1993). These data indicate that in addition to its action on ANP receptors, isatin may also interact with the 5-HT and the dopaminergic systems. More exactly, it was suggested that the anxiogenic-like effects of isatin may be due to stimulation of 5-HT_3 receptors, which are known to function as heteroceptors modulating mesolimbic dopaminergic activity (Bhattacharya and Acharya, 1993; Bhattacharya *et al.*, 1996a). However, it is worth mentioning that the results from the latter interaction study appear not to be consistent with the lack of effect of isatin at 5-HT_3 , D_1, and D_2 receptors, and on the 5-HT reuptake system, as revealed by the above-mentioned binding study (Glover *et al.*, 1995). The reasons for this inconsistency are not clear yet. Further studies with isatin are required to characterize more fully the mechanisms underlying its behavioral effects in anxiety models.

In conclusion, it is clear from the above studies that NPs display anxiolytic-like activity. However, caution is warranted as these effects have been obtained in a limited number of anxiety models. Clearly, the anxiety-reducing potential of these compounds must be evaluated in tests other than the elevated plus-maze. This test has been shown to be particularly remarkable for the variability in the pattern of results that has been reported for a wide range of psychoactive drugs (Griebel, 1995; Hogg, 1996). Moreover, these results will need to be confirmed by laboratories other than that of Bhattacharya and Bíró's groups, which investigated in great part the effects of these drugs.

3. PERSPECTIVES AND SUMMARY

The synopsis of preclinical findings involving CCK, CRF, NPY, TK, NPs, and their receptor ligands in animal models of anxiety or stress strongly suggests that the pharmacological manipulation of these neuropeptides may provide novel avenues for the treatment of anxiety disorders.

Although results obtained with CCK receptor antagonists have been highly variable in animal studies, and clinical trials with some of these agents in GAD and panic disorder have been unsuccessful so far, it is much too soon to draw negative conclusions about their potential in the treatment of anxiety disorders. Experimental models pharmacologically validated by BZs appear to be of limited utility when investigating the effects of CCK receptor antagonists. The development of test procedures that may model aspects of anxiety other than those seen in GAD should allow a more precise evaluation of the anxiety-reducing properties of these compounds, and possibly indicate in which anxiety disorder they may be used. It is also worth mentioning that the drugs tested in clinical trials had poor bioavailability and brain penetration. Clinical investigations using CCK receptor antagonists with better pharmacokinetic characteristics will hopefully permit us to draw a clearer picture of the potential of these compounds as anxiolytics.

The clear evidence that exogenously administered CRF produces physiological and behavioral modifications resembling those observed in animals in response to stress, taken together with the observation that CSF levels of CRF are elevated in patients with OCD and post-traumatic stress disorder, indicate that CRF receptor antagonists may represent novel anxiolytic and/or anti-stress drugs. While stable peptide antagonists may be considered, their usefulness is limited because of inappropriate pharmacokinetics. However, random screening of large chemical libraries and structural modification has enabled the identification of several classes of nonpeptide CRF receptor antagonists that offer clear advantages over the peptide antagonists, as they are metabolically stable and capable of crossing the blood-brain barrier (Christos and Arvanitis, 1998). These compounds should be considered to be highly promising in the treatment of anxiety disorders manifesting hypersecretion of CRF.

Whereas there is little clinical evidence so far indicating that NPY might be involved in human anxiety, the anxiolytic-like effects observed after central administration of NPY or related fragments in a variety of animal models are compelling. However, the discovery of nonpeptide NPY receptor agonists is a prerequisite for a better understanding

of the pathophysiological role of this neuropeptide in the CNS and, ultimately, for the development of NPY anxiolytics.

Results obtained with NK_2 receptor antagonists and NPs in animal models of anxiety provide some evidence that TKs and NPs might be involved in the modulation of anxiety-related behaviors. However, these results must be confirmed with tests other than those based on exploratory behavior. Furthermore, while several selective nonpeptide NK receptor antagonists are now available, nonpeptide NP receptor ligands are still lacking, thereby hindering the development of NP ligands as anxiolytics.

4. CONCLUSION

The above findings strongly suggest that synthetic neuropeptide receptor ligands may have the potential to become an alternative to BZs for the treatment of anxiety disorders. However, the challenge of devising new drugs based on these peptides is difficult and requires much research effort in rational drug-design strategies and screening of large compound libraries.

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