Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders

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The health burden of stress-related diseases, including depression and anxiety disorders, is rapidly increasing, whereas the range of available pharmacotherapies to treat these disorders is limited and suboptimal with regard to efficacy and tolerability. Recent findings support a major role for neuropeptides in mediating the response to stress and thereby identify neuropeptide systems as potential novel therapeutic targets for the treatment of depression and anxiety disorders. In preclinical models, pharmacological and/or genetic manipulation of substance P, corticotropin-releasing factor (CRF), vasopressin, neuropeptide Y and galanin function alters anxiety- and depression-related responses. Recently, specific and highly potent small-molecule neuropeptide receptor agonists and antagonists have been developed that can readily cross the blood–brain barrier. Clinical assessment of several compounds is currently underway, with antidepressant efficacy confirmed in double-blind, placebo-controlled trials of tachykinin NK_1 (substance P) receptor antagonists, and preliminary evidence of antidepressant activity in an open-label trial of a CRF_1 receptor antagonist.

The pathophysiology of depressive illness and anxiety disorders is thought to involve both endogenous predisposing factors and a dysregulated response to stress [1]. The pharmacological treatment of mood and anxiety disorders is dominated by drugs that directly target monoamine or GABA neurotransmitter systems. Monoamine reuptake inhibitors are first-line treatments for depression and are also, along with benzodiazepines, routinely prescribed for anxiety disorders [2]. Current antidepressant treatments have a delayed onset of therapeutic action, and a significant number of patients are non-responsive. Moreover, many patients discontinue treatment with monoamine reuptake inhibitors because of adverse side-effects, including nausea, sexual dysfunction, anorexia, sweating, asthenia (loss or lack of strength) and tremor. The tolerability of benzodiazepine anxiolytics is reduced by sedation, cognitive impairment and dependence. Attempts are currently being made to develop second- or third-generation versions of these drugs (e.g. by targeting subtypes of 5-HT or $GABA_A$ receptors) to lessen the severity of side-effects [2]. An important complementary strategy is to identify novel treatment approaches that target other neurotransmitters and neuromodulators in the brain.

Neuropeptides are attractive therapeutic targets for depression and anxiety disorders [3]. Neuropeptides are short-chain amino acid neurotransmitters and neuromodulators, often localized in brain regions that mediate emotional behaviors and the response to stress [4]. Progress in identifying the role of neuropeptides in stress has been facilitated by recent developments in screening for selective small-molecule neuropeptide ligands that cross the blood–brain barrier. Rodents with mutations in genes encoding neuropeptides and their receptors have been developed and the clinical efficacy of promising compounds has been assessed in patient populations. The list of neuropeptides implicated in stress-related functions is ever increasing. Of these neuropeptides, tachykinins [substance P (SP) and neurokinin A], corticotropin-releasing factor (CRF), vasopressin and neuropeptide Y have been studied extensively, and the involvement of other neuroactive peptides such as galanin has received recent attention. In this article, we consider recent developments in this rapidly advancing field. Table 1 summarizes relevant behavioral abnormalities of various neuropeptide receptor null mutant mice and the behavioral effects of selective small-molecule neuropeptide receptor antagonists.

Substance P

Since its discovery in the 1930s, SP has been one of the most extensively studied neuropeptides. SP is an 11 amino acid peptide belonging to the tachykinin family; it mediates its biological actions through G-protein-coupled tachykinin (NK_1) receptors. During decades of research to map the distribution of SP, there has been much

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 0165-6147/$ - see front matter doi:10.1016/j.tips.2003.09.011

Table 1. Neuropeptide receptor targets for stress-related disorders[a,b]

Receptor targeted	Null mutant mouse phenotype	Selective small-molecule antagonists[c]	Preclinical effects	Effects in clinical trials for depression
NK_1	Anxiolytic-like, antidepressant-like [16,21]	Aprepitant (MK0869), CP122721, L759274, L760735, NKP608, RP67580, SSR240600	Anxiolytic-like, antidepressant-like [5,13–19]	Antidepressant efficacy demonstrated for aprepitant (MK0869) [5], L759274 [6], CP122721[d]
CRF_1	Anxiolytic-like, antidepressant-like [25]	Antalarmin, CRA1000, CRA1001, CP154256, DMP696, NBI27914, R121919, R278995 (CRA0450), SC241, SSR125543A	Anxiolytic-like, antidepressant-like [26–28,32,33]	Antidepressant activity in open-label trial without placebo control demonstrated for R121919 [34]
Vasopressin V_{1b}	Hypo-aggressive [50]	SSR149415	Anxiolytic-like, antidepressant-like [47–49]	–
NK_2	Not determined	GR100679, GR159897, SR48968, SR144190	Anxiolytic-like, antidepressant-like [7]	Antidepressant activity currently being assessed for SR48968
NPY Y_1	Not determined	BIBO3304	Blocks anxiolytic-like effects of NPY [55]	Not determined
NPY Y_2	Anxiolytic-like [62]	BIIE0246	Anxiolytic-like, antidepressant-like [56,57]	Not determined
NPY Y_5	Not determined	CGP71683A, L152804	Partially blocks anxiolytic-like effects of NPY [56]	Not determined

[a]Abnormal anxiety- and antidepressant-related phenotypes in neuropeptide receptor null mutant mice are listed. Preclinical and (where available) clinical effects of target-selective small-molecule antagonists are also shown.
[b]Abbreviations: CRF, corticotropin-releasing factor; NK_1, tachykinin receptor for substance P; NK_2, tachkinin receptor for neurokinin A; NPY, neuropeptide.
[c]See Chemical names.
[d]Unpublished data presented by P.B. Chappel at the Association for European Psychiatry congress, Stockholm in May 2002.

speculation concerning its proposed physiological roles in inflammation, pain, gastrointestinal and respiratory function, stress responses and emesis. Only since the development of highly selective NK_1 receptor antagonists in the past decade has it been possible to test these hypotheses. Preclinical evidence supporting a major role of the SP–NK_1 receptor system in stress-related behaviors has guided the clinical development of NK_1 receptor antagonists. The antidepressant efficacy of the first NK_1 receptor antagonist to be developed clinically, MK0869 (Aprepitant; see Chemical names)), was originally demonstrated in patients with major depression and high anxiety [5], and has recently been replicated with a second compound, L759274 [6]. NK_1 receptor antagonists are generally well tolerated, and might be associated with less nausea and sexual dysfunction than some currently used antidepressants. Aprepitant is currently in Phase III clinical trials for depression. Another member of the tachykinin family, neurokinin A, which acts through NK_2 receptors, is also under investigation for its potential role in depression and anxiety disorders [7], and a clinical trial of an NK_2 receptor antagonist in depression is ongoing. There are marked species differences in the distribution of tachykinin receptors, with NK_1 receptors being the predominantly expressed tachykinin receptor in human brain [8].

Elucidation of the role of SP in centrally mediated stress responses began with neuroanatomical studies mapping the expression of SP and NK_1 receptors in neural circuits involving the amygdala, hypothalamus, hippocampus and periaqueductal gray (Figure 1a). The concentration of SP is altered in these brain regions in response to noxious or aversive stimulation. For example, maternal separation in guinea-pigs causes the release of SP in the amygdala [5], a key brain region that orchestrates endocrine, respiratory, cardiovascular and behavioral stress responses. In addition to its effects in limbic brain regions, SP also has a unique anatomical relationship with monoamine neurotransmitters through which clinically used antidepressant drugs mediate their therapeutic effects. In the human brain, ~50% of 5-HT-containing neurons in the dorsal raphe nucleus (DRN) coexpress SP [9]. Pharmacological blockade or genetic deletion of NK_1 receptors causes an increase in the firing rate of DRN neurons without increasing the extracellular efflux of 5-HT in the cerebral cortex [10,11]. This might be mediated via blockade of inhibitory SP-mediated pathways such as that arising in the habenula [11]. NK_1 receptor antagonists also increase the burst firing of noradrenaline-containing neurons in the locus coeruleus [12], providing another important anatomical site for their psychotropic effects.

Central injection of SP elicits a range of behavioral and cardiovascular stress responses in rats and guinea-pigs. These include an anxiogenic profile on the elevated plus maze [13], potentiation of the acoustic startle response [14], distress vocalizations and escape behavior [5], and cardiovascular changes resembling the defense response to threatening stimuli [15]. Conversely, centrally active NK_1 receptor antagonists, such as L760735, an analog of Aprepitant, exhibit antidepressant-related and anxiolytic-like activity in a range of animal models, notably: reduced aggression in the resident-intruder test [16]; inhibition of distress vocalizations [5,16]; increased glucose intake in the chronic mild stress paradigm [17]; increased social interaction [18]; and increased time spent on the aversive arms of the elevated plus maze [19]. These observations are consistent with reduced anxiety-like behavior of NK_1 receptor null mice as evidenced by their reduced aggression [20], attenuated stress-induced vocalization

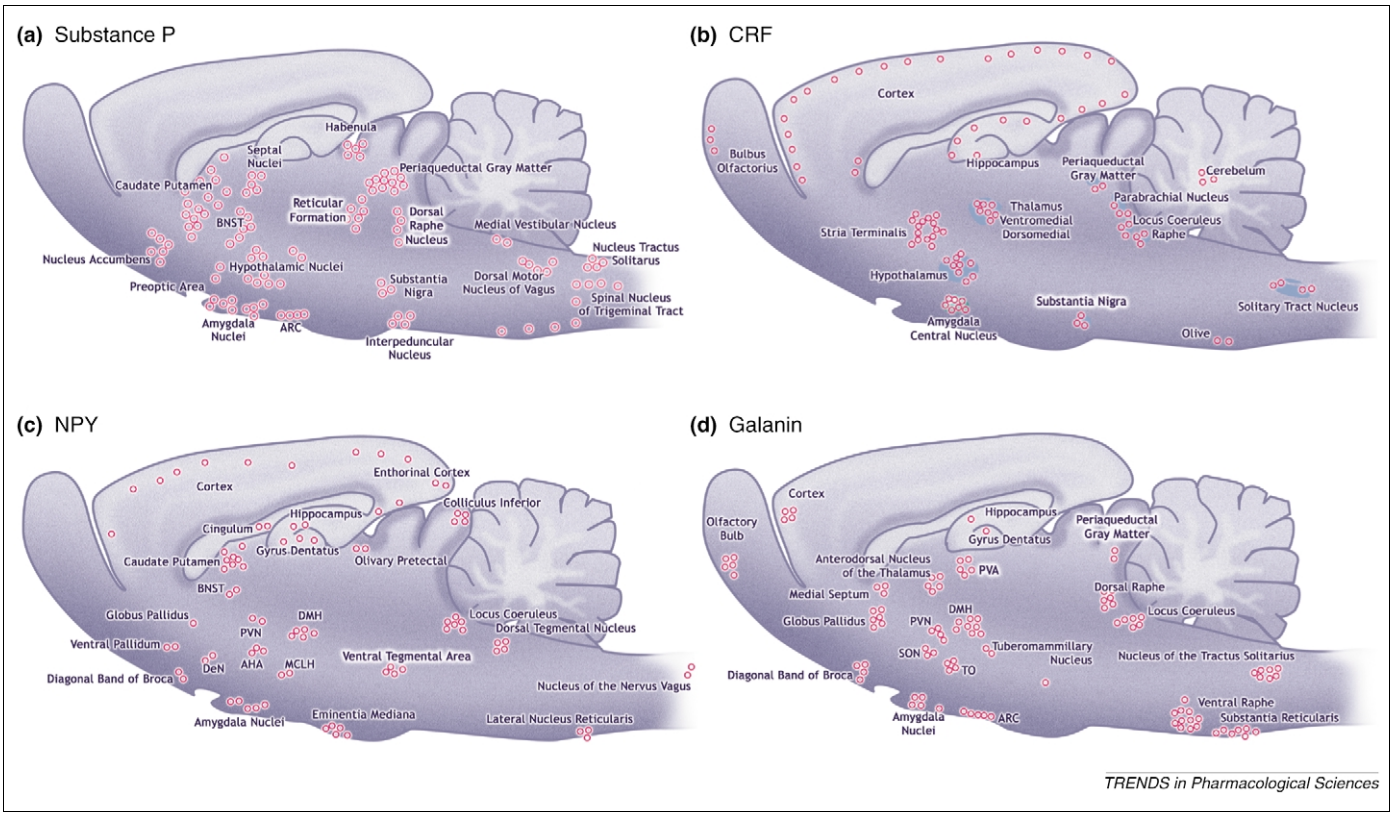

Figure 1. The neuropeptides substance P (SP), corticotropin-releasing factor (CRF), neuropeptide Y (NPY) and galanin are densely localized in rat brain regions that process emotion and the response to stress. (a) SP-like immunoreactive neurons are found in regions including the hypothalamus, amygdala, bed nucleus of the stria terminalis (BNST), habenula, periaqueductal gray matter, nucleus accumbens and dorsal raphe nucleus (adapted from [88]). (b) CRF-like immunoreactivity is seen in regions including the hypothalamus, amygdala, BNST and cortex (adapted from [89]). (c) NPY-like immunoreactive neurons are detected in regions including the hypothalamus, hippocampus, amygdala, cortex, ventral tegmental area and locus coeruleus (adapted from [89]). (d) Galanin-like immunoreactive neurons are found in regions including the hypothalamus, amygdala, periaqueductal gray matter, raphe nuclei and locus coeruleus (adapted from [89]). Abbreviations: AHA, anterior hypothalamic area; ARC, arcuate nucleus; DeN, dorsoendopiriform nucleus; DMH, dorsomedial nucleus of the hypothalamus; MCLH, nucleus magnocellularis of the lateral hypothalamus; PVA, paraventricular nucleus of the thalamus; PVN, paraventricular nucleus of the hypothalamus; SON, supraoptic nucleus of the hypothalamus; TO, tractus opticus.

response [16,21] and increased time spent on the open arms of an elevated plus maze [21]. Interestingly, although established antidepressants and anxiolytics can cause motor impairment or sedation in animals, these effects were not seen with NK_1 receptor antagonists.

Corticotropin-releasing factor

The 41 amino acid neuropeptide CRF initiates the hypothalamic–pituitary–adrenal (HPA) axis response to stress, and has been the subject of intense investigation in the pathophysiology and treatment of depression and anxiety disorders. In the mammalian brain, the CRF system comprises four CRF-related peptides (CRF, and urocortin 1, 2 and 3) and two G-protein-coupled CRF receptor subtypes {CRF_1 and CRF_2 receptors [with 2(a), 2(b) and 2(c) splice variants]}. In addition to a major projection from the paraventricular nucleus of the hypothalamus (PVN) to the pituitary corticotropes, CRF-containing neurons and receptors are also found in brain areas involved in stress responses, including the amygdala, lateral septum, locus coeruleus and brainstem raphe nuclei [22] (Figure 1b; Figure 2a).

Abnormal HPA activity has been implicated in a variety of conditions related to stress, including HPA overactivation in depression and anxiety, but also eating and substance use disorders, irritable bowel syndrome, inflammation and cardiovascular dysfunction. Infusion of CRF fragments into the rodent brain, or constitutive transgenic overexpression of CRF in mice, recapitulates some of the behavioral and neuroendocrine consequences of exposure to stress, such as increased anxiety-like behavior and HPA dysfunction [23,24]. Preclinical studies have begun to shed light on how CRF receptors mediate these effects.

CRF_1 and CRF_2 receptor subtypes show distinct expression patterns and binding characteristics [22]. There is now compelling evidence that CRF_1 receptors play an important role in mediating the HPA response to stress and the extrahypothalamic mediation of stress-related behaviors. CRF_1 receptor null mutant mice display decreased anxiety-like behaviors in various tests (e.g. light–dark exploration) and blunted HPA responses to stress, whereas CRF_1 receptor antagonists induce anxiolytic- and antidepressant-like effects in rodents and non-human primates [25–28] (Table 1). Although non-peptide CRF_1 receptor antagonists can suppress glucocorticoids under certain non-stressful conditions [28] (probably via adrenal CRF_1 receptors), these compounds appear to selectively block CRF- and stress-induced adrenocorticotropin (ACTH) release [28–30] without disturbing basal ACTH release [28,29]. This is consistent with observations that a full ACTH response can still be obtained with partial CRF_1 receptor occupancy [31]. Moreover, the anxiolytic-like effects of CRF_1 receptor antagonists in rodents might be contingent upon levels

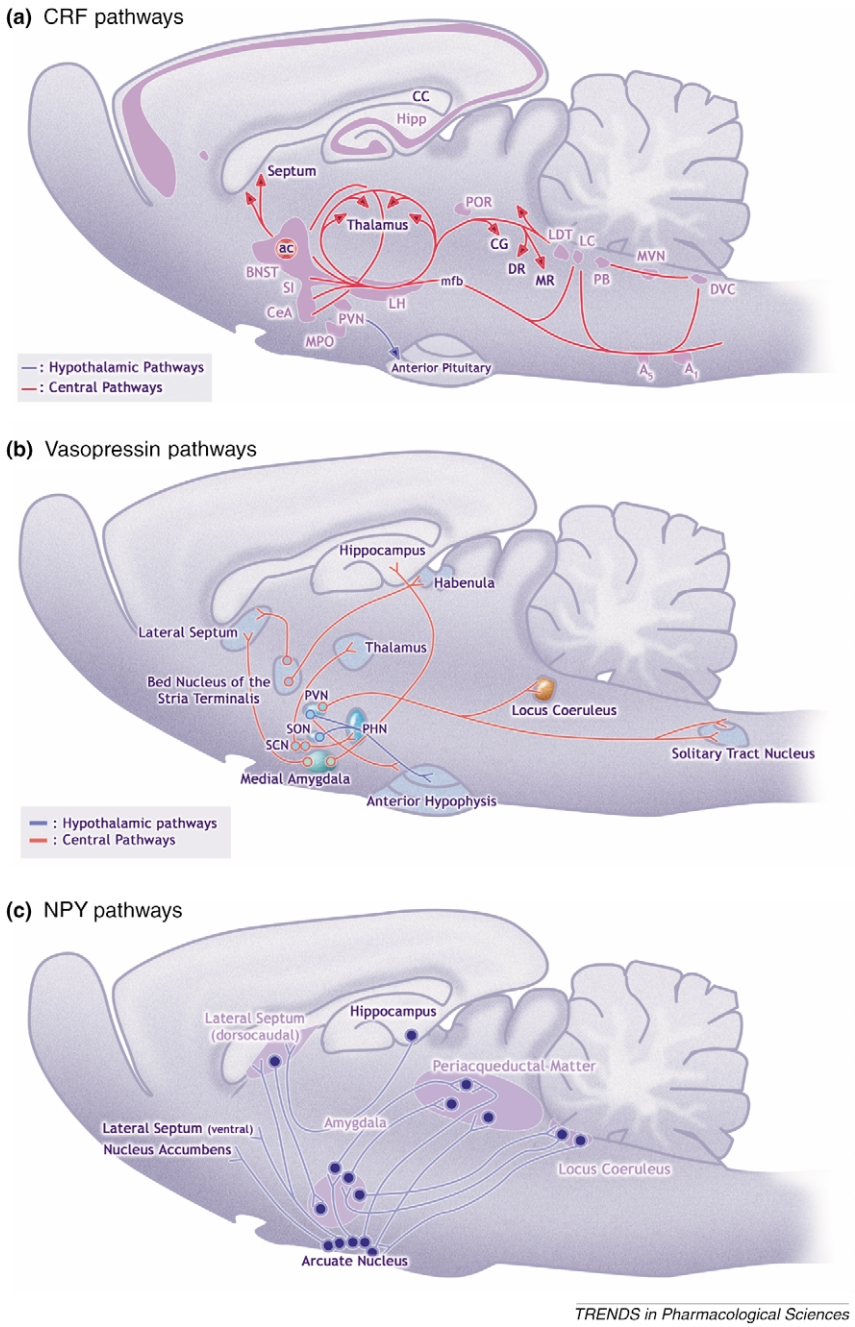

Figure 2. Corticotropin-releasing factor (CRF), vasopressin and neuropeptide Y (NPY) pathways in rat brain regions that process emotion and the response to stress. (a) CRF is secreted from the parvocellular paraventricular nucleus (PVN) into the hypothalamohypophyseal portal vessels and liberates adrenocorticotropin (ACTH) and β-endorphin from the anterior pituitary. Central CRF pathways originate, for example, from the central nucleus of the amygdala (CeA) to the bed nucleus of the stria terminalis (BNST), from the CeA and BNST to the periaqueductal gray matter and autonomic brain stem regions, and the locus coeruleus (LC), from the BNST and dorsal raphe nucleus (DR) to the PVN, and from the hypothalamus to the lateral septum (adapted from [90]). Of note, other CRF-related peptides such as urocortin 1, 2 and 3 show an expression pattern that is different from CRF (not shown). The major site of urocortin 1 expression is the Edinger-Westphal nucleus, whereas urocortin 2 mRNA is expressed, for example, in the arcuate hypothalamic nucleus and the LC, and urocortin 3 is expressed highly in hypothalamic areas and the medial amygdala. (b) Hypothalamic vasopressin pathways originate from the hypothalamus and project to the pituitary, or LC and solitary tract nucleus. Central vasopressin pathways project from the BNST to the septum and the habenula, and from the amygdala to the septum and hippocampus. (c) NPY pathways originating in the arcuate nucleus project to the lateral septum, amygdala, periacqueductal gray matter and LC. Major NPY-containing neurons in the amygdala also innervate the periacqueductal gray matter and LC (adapted from [51]). Abbreviations: A_1, A_5, noradrenaline-containing cell groups; ac, anterior commissure; CC, corpus callosum; CG, central gray matter; DVC, dorsal motor nucleus of the vagus; Hipp, hippocampus; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamus; mfb, medial forebrain bundle; MPO, median preoptic area; MR, midbrain raphe nucleus; MVN, medial vestibular nucleus; PB, parabrachial nucleus; PHN, posterior hypothalamic area; POR, perioculomotor nucleus; SCN, suprachiasmatic nucleus; SI, substantia innominata; SON, supraoptic nucleus of the hypothalamus.

of stress. For example, some studies have shown that the anxiolytic-like effects of CRF_1 receptor antagonists are more pronounced in rats that have been pre-exposed to stressors such as immobilization, forced swimming and social defeat, with minor effects on locomotor activity, coordination and sedation [27,32,33]. These findings lend support to the hypothesis that CRF_1 receptor antagonists might be capable of blocking pathological CRF-mediated

stress responses without producing unwanted side-effects caused by a general suppression of HPA activity (e.g. metabolic abnormalities).

Preliminary data regarding the potential clinical utility of CRF_1 receptor antagonists are encouraging [34]. In a small, open-label clinical trial, symptoms of anxiety and depression in patients with major depression were reduced during treatment with the CRF_1 receptor antagonist R121919 [34]. Larger, double-blind, placebo-controlled studies are needed to establish the efficacy of these compounds in treating mood and anxiety disorders.

Further studies will also clarify the role of CRF_2 receptors. These receptors do not seem to play a major role in the activation of the HPA axis by stress, but might maintain the HPA response [35], possibly by acting as autoreceptors on CRF-containing neurons in the PVN (although a different situation might exist in humans and non-human primates than in rodents). Furthermore, antisense knockdown and peptidergic antagonism of CRF_2 receptors, particularly in the lateral septum, produces anxiolytic- [36] and antidepressant-like [37] effects in rodents. However, this anti-stress profile of CRF_2 receptor antagonism contrasts with the anxiogenic-like phenotype found in CRF_2 receptor null mutant mice [35]. Additional research is needed to further define the role of CRF receptors in stress and to assess the potential utility of CRF receptor antagonists across a range of disorders related to stress.

Vasopressin

The nonapeptide vasopressin, synthesized in the PVN and supraoptic nucleus, is well known for its role on fluid metabolism. Vasopressin is also a key regulator of the HPA axis. Stress stimulates the release of vasopressin from the median eminence into the pituitary portal circulation where it strongly potentiates the effects of CRF on ACTH release [38].

Extrahypothalamic vasopressin-containing neurons have been characterized in the rat, notably in the medial amygdala and the bed nucleus of the stria terminalis (BNST) [39] (Figure 2b). Vasopressin released from these neurons exerts its effects via a dense localization of vasopressin receptors (V_{1a} and V_{1b} receptors) expressed mainly in limbic areas and in the hypothalamus [40]. This pattern of distribution suggests that vasopressin might exert a modulatory role on limbic function and responses to stress. In support of this assertion, vasopressin applied, for example, intracerebroventricularly or to the lateral septum has been shown to affect cognition, social and anxiety-like behaviors in rodents [41]. Moreover, abnormalities in vasopressin expression or receptor activity have been found in both clinical depression and rodent genetic models of depression [42,43], whereas vasopressin release has been shown to predict anxiety reactions to stress provocation in healthy volunteers [44]. These findings have led to the suggestion that HPA axis dysregulation in depression and anxiety disorders might be associated with a shift towards increased vasopressin-mediated control of the axis [45,46]. As such, vasopressin receptor antagonists might represent potential agents for the treatment of these disorders.

This hypothesis is supported by the finding that the non-peptide V_{1b} receptor antagonist SSR149415 exerts marked anxiolytic-like and antidepressant-like effects in rodents [47,48]. Interestingly, although the antidepressant-like activity of the compound was comparable to that of reference antidepressants, the overall profile displayed in anxiety tests was different from that of classical anxiolytics, such as benzodiazepines. Benzodiazepines were active in a wide range of anxiety models, whereas SSR149415 displayed clear-cut effects only in the more stressful test situations. These findings have been extended to show that antagonism of V_{1b} receptors in the lateral septum and the central nucleus of the amygdala plays a predominant role in the antidepressant-like but not the anxiolytic-like effects of the compound [49]. In contrast to the marked effects of pharmacological V_{1b} receptor antagonism, mice with a targeted mutation in the V_{1b} receptor show reduced aggression but normal anxiety-like behavior and neuroendocrine stress responses, possibly as a result of compensatory changes at the level of the V_{1a} receptor or CRF system [50]. In this context, studies on the potential role of the V_{1a} receptor in stress are awaited. Taken together, current research suggests that blockade of central V_{1b} receptors might represent a novel therapeutic strategy for the treatment of stress-related psychiatric disorders.

Neuropeptide Y

Neuropeptide Y (NPY) is the ancestor of a peptide family that in mammals also includes pancreatic polypeptide (PP) and peptide YY (PYY). In addition to a role as a sympathetic co-transmitter, NPY is abundantly expressed in numerous brain areas, including the locus coeruleus, hypothalamus, amygdala, hippocampus, nucleus accumbens, and neocortex (Figure 1c; Figure 2c). Central NPY colocalizes with noradrenaline, GABA, somatostatin and agouti-related protein [51]. Actions of NPY are mediated through heterogeneous G-protein-coupled receptors, among which Y_1, Y_2 and Y_5 receptor subtypes mediate CNS effects. Of note, Y_2 receptors can act as a presynaptic NPY autoreceptor; their blockade potentiates the release of endogenous NPY and thus subsequent postsynaptic actions.

A crucial role for NPY in feeding, circadian rhythms, cognition and seizure activity has been demonstrated. Furthermore, studies in humans have suggested a link between low levels of NPY and increased risk for mood and anxiety disorders, a suggestion supported by data from preclinical experiments. In rodent models, central NPY is expressed and released following stress, and attenuates the behavioral consequences of stress [51–54]. Activation of Y_1 receptors or Y_5 receptors in the basolateral amygdala produces dose-related anxiolytic-like effects in rodents [55]. By contrast, presumably through presynaptic inhibition of endogenous NPY release, Y_2 receptor activation is anxiogenic like [56,57]. Recent studies in rodents have extended these observations to demonstrate antidepressant-like effects of centrally administered Y_1 receptor agonists [58].

Studies using recently available mutant rodent lines further support an anxiolytic and antidepressant role for NPY. Notably, mutant mice lacking NPY show increased

anxiety-like behavior [59]. A full picture of anxiety- and antidepressant-related phenotypes in NPY receptor null mutant mice is not yet available, but recent data from Y_2 receptor null mutants support an anti-stress action of endogenous NPY [60]. This is in agreement with studies of stress-related behaviors in a transgenic rat with selective NPY overexpression within the hippocampus [61]. These animals display no overt phenotype under baseline conditions and have a normal neuroendocrine response to stress. However, in a strikingly specific phenotype, they are resistant to the anxiety-like consequences of exposure to stress. The mechanisms by which NPY exerts anti-stress effects remains unclear but might relate to inhibition of glutamate release and potentiation of GABA-mediated neurotransmission [62].

Finally, there is an emerging relationship between NPY, stress-related behavior and alcohol intake. Voluntary ethanol consumption is elevated in NPY and Y_1 receptor null mutant mice, whereas either NPY overexpression or potentiation of NPY signaling through blockade of Y_2 receptors suppresses rodent alcohol consumption [63–65]. In addition, in a genetic model of alcohol dependence, a major quantitative trait locus (QTL) for alcohol preference has been found to map to markers within the gene encoding NPY [66]. Thus, alcohol dependence, which is frequently comorbid, and possibly pathophysiologically related to depression and anxiety disorders, emerges as a novel potential indication for compounds targeting NPY receptors.

Galanin

The 29–30 amino acid neuropeptide galanin coexists with noradrenaline in locus coeruleus neurons and with 5-HT in the DRN. The neuropeptide has been shown to act as an inhibitory neuromodulator of these (and other) neurotransmitters in the rodent brain [67,68]. Although its distribution appears to vary somewhat across species [69], galanin and its receptors are found in limbic regions, including the amygdala, BNST, hippocampus and hypothalamus of the rat brain [70,71] (Figure 1d). The differential localization of the three known G-protein-coupled galanin receptor subtypes (GAL1, GAL2 and GAL3) in the brain and periphery suggests that individual galanin receptor subtypes might mediate different functional effects of this neuropeptide.

Central administration of galanin in rodents produces effects on cognition, feeding, sexual behavior, seizures, nerve regeneration and nociception [72]. Galanin also mediates neural, neuroendocrine and sympathetic responses to stress. Galanin gene expression is upregulated in the rat hypothalamus, amygdala and locus coeruleus by chronic forms of immobilization, exercise and social stress, but not by putatively less stressful manipulations [73]. Moreover, exogenous galanin and peptidergic galanin receptor antagonists alter anxiety-like behavior in rats, albeit in a brain region- and task-specific manner [74,75]. For example, endogenous galanin activity in the amygdala has been associated with anxiogenic-like effects under conditions of stress and high noradrenergic activity [76]. The latter finding is consistent with preliminary evidence that mutant mice with a conditional overexpression of galanin in noradrenaline-containing neurons are relatively insensitive to the anxiogenic-like effects of noradrenaline challenge [77], and that GAL1 receptor null mutant mice selectively show increased anxiety-like behavior under stressful test conditions [72].

The available data from preclinical behavioral studies suggest that targeting the galanin system might be of therapeutic benefit in anxiety disorders where noradrenergic overactivity is a putative pathophysiological factor (e.g. panic disorder and post-traumatic stress disorder). Conversely, normalizing deficient monoamine-mediated neurotransmission in mood and anxiety disorders is also a potential target for galanin receptor ligands. Thus, blocking the inhibitory effects of galanin on monoamine neurotransmission with galanin receptor antagonists would be predicted to mimic or augment the action of antidepressants. In this context, central administration of galanin has recently been found to attenuate antidepressant-induced increases in rat forebrain levels of 5-HT and noradrenaline [78]. Much work is still needed to determine whether galanin receptor ligands (acting at which galanin receptor subtypes) exert antidepressant-like and anti-stress actions in preclinical models. This research will be facilitated by the continued engineering of galanin receptor mutant mice and the development of small-molecule galanin receptor subtype-selective ligands [79,80]. Although our understanding of the role of galanin in stress is still at an early stage, this system is one example of a growing number of emerging neuropeptide-based therapeutic targets for stress-related disorders.

Future directions

Figure 1 illustrates the high degree of anatomical overlap in the distribution of neuropeptide neurons in limbic regions of the rat brain. This raises the question of whether these neuropeptides exert common downstream effects on neural systems that mediate stress. Indeed, there is evidence of functional relationships between certain neuropeptides. The intimate relationship between vasopressin and CRF at the level of the HPA axis is probably the best example of this, but there has also been speculation regarding stress-related interactions between CRF, SP, NPY and galanin in the brain [81–84]. However, it is still premature to speculate on whether and how these systems might exert common downstream effects on brain pathways that mediate stress and emotion. Thus, although SP, CRF, vasopressin, NPY and galanin demonstrate important functional interactions with monoamines implicated in the etiology and treatment of stress-related disorders, their effects almost certainly go beyond modulation of these neurotransmitters. Understanding these effects is a central goal of future research in this field.

There are certain characteristics common to neuropeptides that might make them attractive targets for novel therapeutics. Because neuropeptides possess a more discrete neuroanatomical localization than monoamines and GABA, neuropeptide receptor ligands might be expected to produce relatively little disruption of normal physiology. Moreover, there is evidence that the neuronal release of neuropeptides requires higher stimulation

Chemical names

Antalarmin: N-butyl-N-ethyl-[2,5,6,-trimethyl-7-(2,4,6-trimethylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]amine
Aprepitant (MK0869): 2-(*R*)-(1-(*R*)-3,5-bis(trifluoromethyl)-phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorphol
BIBO3304: (*R*)-N(2)-(diphenylacetyl)-N-[4-(aminocarbonyl-aminomethyl)-benzyl]-argininamide trifluoroacetate
BIIE0246: (*S*)-N^2-[[1-[2-[4-[(*R*,*S*)-5,11-dihydro-6(6 *h*)-oxo-dibenz[*b*,*e*]azepin-11-yl]-1-piperazinyl]-2-oxoethyl] cyclopentyl] acetyl]-*N*-[2-[1,2-dihydro-3,5(4*H*)-dioxo-1,2-diphenyl-3*H*-1,2,4-triazol-4-yl]ethyl]-argininamide
CGP71683A: *trans*-naphtalene-1-sulfonic acid [4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-amide hydrochloride
CP122721: (+)-(2*S*,3*S*)-3-(2-methoxy-5-trifluoromethoxy-benzyl)amino-2-phenylpiperidine
CP154256: N-butyl-N-ethyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-7*H*-pyrrolo[2.3-*d*]pyrimidin-4-yl]amine
CRA1000: 2-[N-(2-methylthio-4-isopropylphenyl)-N-ethyl-amino]-4-(4-(3-fluorophenyl)-1,2,3,6-tetrahydropyridin-1-yl)-6-methylpyrimidine
CRA1001: 2-[N-(2-bromo-4-isopropylphenyl)-N-ethylamino]-4-(4-(3-fluorophenyl)-1,2,3,6-tetrahydropyridin-1-yl)-6-methylpyrimidine
DMP696: 4-(1,3-dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-*a*]-1,3,5-triazine
GR100679: cyclohexylcarbonyl-Gly-Ala-(D)Trp-Phe-NMe2
GR159897: (*R*)-1-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-4-methoxy-4-[(phenylsulfinyl)methyl]piperidine
L152804: 2-(3,3-dimethyl-1-oxo-4*H*-1*H*-xanthen-9-yl)-5,5-dimethyl-cyclohexane-1,3-dione
L759274: not available
L760735: (2-(*R*)-(1-(*R*)-3,5-bis(trifluoromethyl)phenyl)ethoxy-4-(5-(dimethylamino-methyl)-1,2,3-triazol-4-yl)methyl-3-(5)-phenyl)morpholine
NBI27914: 2-methyl-4-(N-propyl-N-cycloproanemethyl-amino)-5-chloro-6-(2,4,6-trichloranilino)pyrimidine
NKP608: quinoline-4-carboxylic acid [*trans*-(2*R*,4*S*)-1-(3,5-bis-trifluoromethyl-benzoyl)-2-(4-chloro-benzyl)-piperidin-4-yl]-amide
R121919: 3-[6-(dimethylamino)-4-methyl-pyrid-3-yl]-2,5-dimethyl-N,N-dipropyl-pyrazolo[2,3-*a*]pyrimidin-7-amine
R278995 (CRA0450): 1-[8-(2,4-dichlorophenyl)-2-methyl-quinolin-4-yl]-1,2,3,6-tetrahydropyridine-4-carboxamide benzenesulfonate
RP67580: 2-[1-imino-2-(2-methoxy phenyl) ethyl]-7,7 diphenyl-4 perhydroisoindolone-(3*aR*,7*aR*)
SC241: [3-(2-bromo-4-isopropyl-phenyl)-5-methyl-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl]-bis-(2-methoxy-ethyl)-amine)
SR144190: (*R*)-3-(1-[2-(4-benzoyl-2-(3,4-difluorophenyl)-morpholin-2-yl)-ethyl]-4-phenylpiperidin-4-yl)-1-dimethylurea
SR48968: (S)-N-methyl-N-[4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichlorophenyl) butyl] benzamide
SSR125543A: 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine hydrochloride
SSR149415: (2*S*,4*R*)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)-sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidinecarboxamide
SSR240600: (*R*)-2-(1-[2-[4-[2-[3,5-bis(trifluoromethyl)-phenyl]acetyl]-2-(3,4-dichloro phenyl)-2-morpholinyl]ethyl]-4-piperidinyl)-2-methylpropanamide

frequencies than that required by monoamine neurotransmitters colocalized in the same neuron [85,86]. This might explain why, in some cases, manipulation of CRF, vasopressin, NPY and galanin function has been found to selectively impact behavioral responses under conditions of high, but not low, stress. Thus, pharmacological alteration of neuropeptide function might normalize pathological activity in circuits mediating stress, such as the HPA axis, without producing unwanted side-effects [4]. Moreover, antagonists might be less likely than agonists to produce tolerance and dependence. Indeed, drugs that are antagonists at CRF, vasopressin, NPY and galanin receptors might have a particularly low side-effect burden because such compounds would not be expected to disrupt normal physiology in the absence of neuropeptide release. Preliminary clinical data appear to be encouraging in this regard.

Several ligands that target neuropeptide receptors are currently undergoing clinical evaluation to determine whether they provide efficacious alternatives to existing drug treatments for depression and anxiety disorders. Establishing the safety, therapeutic efficacy and an acceptable tolerability profile of drugs that target neuropeptides in depression and anxiety disorders would represent a major advance in the treatment of these diseases. The validation of future targets will be facilitated by the generation of mutant rodents to elucidate neuropeptide function, particularly where a paucity of selective, brain-penetrant ligands limits conventional psychopharmacological approaches. The effects of constitutive neuropeptide mutations can be skewed by developmental alterations that compensate for the mutated neuropeptide [87] or cause changes in other systems that confound interpretation of stress-related phenotypes [35]. Therefore, engineering neuropeptide mutations that are limited to specific developmental stages and brain regions, or improving other molecular manipulations (e.g. RNA interference, antisense and viral vector delivery techniques), will be valuable. Once promising targets are identified, a further challenge is the generation of small-molecule neuropeptide receptor ligands that are soluble, bioavailable, brain-penetrant and have a low potential for tachyphylaxis. Although there are important obstacles to surmount, neuropeptide-based therapeutic strategies for depression and anxiety disorders represent a highly promising approach to treating these debilitating conditions.

Acknowledgements
A.H. is supported by the National Institute on Alcohol Abuse and Alcoholism and M.H. by grants from the Swedish Medical Research Council and the European Community.

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