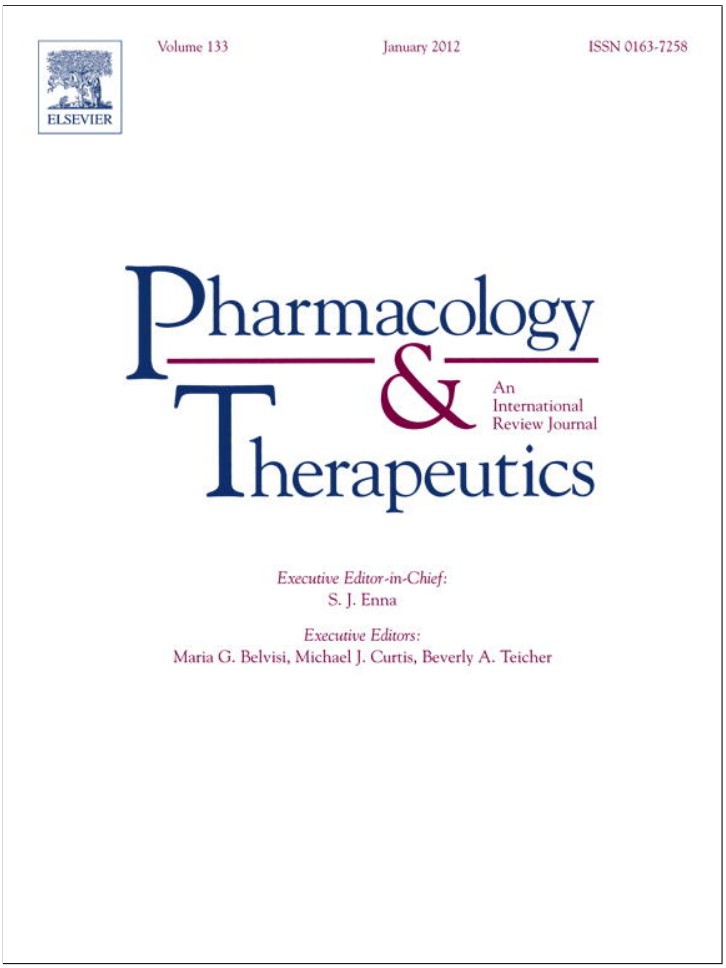

Pharmacology & Therapeutics 133 (2012) 116–123

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Is there still a future for neurokinin 3 receptor antagonists as potential drugs for the treatment of psychiatric diseases?

Guy Griebel *, Sandra Beeské

Sanofi, Chilly-Mazarin, France

ARTICLE INFO

Keywords:
Anxiety disorders
Major depressive disorder
Neurokinin 3 receptor
Neuropeptide
Schizophrenia
Tachykinin

ABSTRACT

Selective non-peptide antagonists for the neurokinin 3 (NK_3) receptor first became available about twenty years ago. Although the understanding of the role of the NK_3 receptor in the brain has been greatly complicated by marked species differences in its distribution and by pharmacological heterogeneity, studies with brain-penetrant non-peptide NK_3 receptor antagonists in animals have indicated that these compounds may find utility in a number of psychiatric diseases, including schizophrenia, anxiety and depressive disorders. However, clinical studies with selective NK_3 receptor antagonists in these psychiatric conditions have been disappointing and they were unable to confirm the promising therapeutic potential from animal studies, thereby questioning the therapeutic utility of these compounds for CNS disorders. The purpose of this article is to provide a critical overview of the available data on NK_3 receptor antagonists in the psychiatry research and development field, by reviewing the behavioral and neurochemical effects of these agents in both preclinical and clinical studies.

Contents

1. Introduction

At least five mammalian tachykinins, namely substance P (SP), neurokinin A (NKA), neurokinin B (NKB), neuropeptide K and neuropeptide γ have been identified in the periphery and in the central nervous system (CNS) (Helke et al., 1990; Otsuka & Yoshioka, 1993). They all share the common C-terminal sequence Phe-X-Gly-Leu-Met-NH_2, where X is either Phe (for SP) or Val. This portion of the peptides has been identified as being critical for receptor recognition and activation. Mammalian tachykinins are the products of the preprotachykinin gene I, except NKB which derives from the preprotachykinin II gene (Bonner et al., 1987; Carter & Krause, 1990). These neuropeptides exert a plethora of biological effects, including smooth muscle contraction and relaxation, vasodilatation, secretion, activation of the immune system, pain transmission and neurogenic inflammation, and are implicated in a broad range of CNS disorders. These effects are mediated predominantly by three G-protein coupled receptors containing seven transmembrane domains, termed NK_1, NK_2 and NK_3. Under certain conditions, neurokinin receptors demonstrate limited selectivity for SP, NKA and NKB, and it is possible that their actions could be mediated by interaction with their less preferred receptors. However, it is widely acknowledged that SP activates mostly the NK_1 receptor, while NKA and NKB are naturally occurring agonists for the NK_2 and NK_3 receptors, respectively (Maggi, 1995).

Abbreviations: 5-HT, serotonin; BPRS, Brief Psychiatric Rating Scale; cAMP, cyclic adenosine monophosphate; CGI, Clinical Global Impressions; CHO, Chinese hamster ovary; CNS, central nervous system; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; GABA, γ-aminobutyric acid; i.c.v., intracerebroventricular; NK, neurokinin; NKA, neurokinin A; NKB, neurokinin B; PANSS, Positive and Negative Syndrome Scale; PPI, prepulse inhibition; SP, substance P.

* Corresponding author at: Sanofi, 1 avenue Pierre Brossolette, 91385 Chilly-Mazarin, France. Tel.: +33 1 60 49 54 30.
E-mail address: guy.griebel@sanofi.com (G. Griebel).

0163-7258/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2011.09.007

The purpose of this article is to provide a critical overview on the therapeutic potential of NK_3 receptor antagonists in psychiatric diseases, by reviewing the behavioral and neurochemical effects of these agents in both preclinical and clinical studies, with a focus on osanetant, the most extensively studied NK_3 receptor antagonist. For an overview of the therapeutic potential of NK_1 and NK_2 receptor antagonists, the reader is directed towards recently published reviews (Ebner et al., 2009; Munoz & Covenas, 2011; Quartara et al., 2009).

2. The neurokinin 3 receptors and their antagonists

2.1. Distribution of neurokinin 3 receptors in the brain: evidence for species differences

While NK_1 receptors are highly expressed in both the CNS and peripheral tissues, and NK_2 receptors are characterized by a predominant expression in the periphery, NK_3 receptors are found primarily in the CNS. The distribution of NK_3 binding sites in the CNS has been studied in several species including rats, guinea pigs, gerbils and humans, by various techniques: radioligand autoradiography, in situ hybridization and immunohistochemistry. These studies revealed important species differences (Almeida et al., 2004; Buck et al., 1986; Carpentier & Baude, 1996; Dam et al., 1990; Ding et al., 1996; Langlois et al., 2001; Mussap & Burcher, 1990; Pinto et al., 2004; Saffroy et al., 2003; Shughrue et al., 1996; Stoessl & Hill, 1990; Yip & Chahl, 2001). While in rats, guinea pigs and gerbils the NK_3 receptor was similarly distributed within the cerebral cortex, the zona incerta, the medial habenula, the amygdala nuclei, the superior colliculus, the interpeduncular nucleus, the ventral tegmental area, the substantia nigra pars compacta and the dentate gyrus, outside of these structures each species displayed a specific distribution pattern of central NK_3 receptors (Fig. 1). For example, the guinea pig was the only species where NK_3 receptors could be visualized in the lateral septum. The rat differed mainly from the two other species by the absence of detectable binding sites in the thalamus. It is noteworthy that the distribution of NK_3 receptors in the guinea pig brain was similar to that described for human, suggesting that the guinea pig should be the species of choice for pharmacological studies on NK_3 receptors. This idea is strengthened by the observation that the rat NK_3 receptor exhibits a different pharmacological profile than the human NK_3 receptor, while that of the guinea pig and, to a lesser extent, the gerbil, is similar to the human NK_3 receptor (Nguyen et al., 1994; Suman-Chauhan et al., 1994). Moreover, NK_3 receptor antagonists have generally a higher affinity for the human, the gerbil and the guinea pig than for the rat NK_3 receptor (Emonds-Alt et al., 1995).

2.2. Selective non-peptide antagonists for neurokinin 3 receptors

Osanetant (N-[1-[3-[1-benzoyl-3(R)-(3,4-dichlorophenyl)piperidin-3-yl]propyl]-4-phenylpiperidin-4-yl]-N-methylacetamide) was the first potent non-peptide NK_3 receptor antagonist described in the literature (Emonds-Alt et al., 1995). The compound derived from chemical modifications of another dichlorophenylalkylpiperidine, the NK_2 receptor antagonist saredudant (SR48968) (Emonds-Alt et al., 1992). Osanetant potently inhibited the binding of [^{125}I]iodohistidyl-[MePhe^7]-NKB to NK_3 receptors from guinea pig and gerbil brain cortex ($K_i = 0.11$ and 0.42 nM, respectively) and to cloned human NK_3 receptors expressed in CHO cells ($K_i = 0.21$ nM), but was less active on NK_3 receptors from rat brain cortex as indicated by [^{125}I]eledoicin binding ($K_i = 15$ nM) (Oury-Donat et al., 1995). Potent antagonist activity of osanetant at the NK_3 receptor was demonstrated by its ability to inhibit acetylcholine release following activation of the guinea pig ileum NK_3 receptor (Emonds-Alt et al., 1995) and the contractile response of rabbit iris sphincter muscle to the NK_3 receptor agonist senktide (Medhurst et al., 1997). In CHO cells expressing human NK_3 receptors, osanetant antagonized increases in inositol monophosphate formation, arachidonic acid release, cAMP accumulation and intracellular Ca^{2+} concentrations induced by selective NK_3 receptor agonists (Oury-Donat et al., 1995). Electrophysiological experiments in guinea pig locus coeruleus and substantia nigra slices revealed that osanetant antagonized in a concentration-dependent manner the increase in firing rate of noradrenergic and dopaminergic cells, respectively, induced by senktide (Jung et al., 1996; Nalivaiko et al., 1997). In vivo microdialysis experiments in guinea pigs showed that the NK_3 receptor antagonist reduced dose-dependently the increase in norepinephrine and dopamine (DA) release in the striatum, the nucleus accumbens and the prefrontal cortex (norepinephrine and DA) elicited by intracerebroventricular (i.c.v.) or midbrain infusion of senktide (Bert et al., 2002; Jung et al., 1996; Marco et al., 1998). In behavioral experiments in gerbils, osanetant potently inhibited the turning response induced by intrastriatal infusion of senktide, and reversed the reduction of exploration produced by i.c.v. senktide. Importantly, all these antagonistic effects were stereospecific as the inactive (S)-enantiomer, SR142806, was approximately 100-fold less effective than osanetant in inhibiting NK_3 agonist-evoked responses.

The discovery of osanetant was followed soon thereafter with the report of a variety of novel chemical classes of potent, competitive, and selective non-peptide antagonists for the human NK_3 receptor. As of today there are more than 80 patent applications disclosing compounds claimed as NK_3 receptor antagonists with a rich structural diversity (for further details, see Dawson & Smith, 2010; Juhl et al., 2011; Malherbe et al., 2011a; Simonsen et al., 2010). Among the most investigated compounds are talnetant (formerly SB223412) (Sarau et al., 1997), SSR146977 (Emonds-Alt et al., 2002), GSK-256471 (Smith et al., 2009), SB222200 (Sarau et al., 2000) and SB235375 (Hay et al., 2002). They all showed high selectivity for NK_3 versus NK_1 and NK_2 receptors (Table 1), and were without effect in a multitude of assays for various receptors, ion channels and enzymes. They proved to be potent antagonists at the NK_3 receptor, as indicated by their ability to inhibit senktide-induced contraction in the isolated rabbit iris sphincter muscle and NKB-induced Ca^{2+} mobilization in HEK 293 cells expressing the hNK_3 receptor. Peripheral administration of talnetant, GSK256471, SSR146977 and SB222200, but not SB235375 inhibited stereotypies induced by i.c.v. senktide in mice, guinea-pigs or gerbils, indicating that the latter is a low CNS-penetrant compound (Dawson et al., 2010; Emonds-Alt et al., 2002; Hay et al., 2002; Nordquist et al., 2010; Sundqvist et al., 2007).

3. Therapeutic utility of neurokinin 3 receptor antagonists in psychiatric diseases

3.1. Schizophrenia

Experimental evidence indicates that NK_3 receptors play a key role in dopaminergic function in the midbrain. Since excessive dopaminergic function is believed to be responsible for some of the symptoms of schizophrenia, it was hypothesized that tachykinins may be involved in the pathophysiology of this condition (for recent reviews, see Dawson & Smith, 2010; Simonsen et al., 2010; Spooren et al., 2005). NK_3 receptors are found predominantly in the substantia nigra and the ventral tegmental area, brain regions that have a high concentration of DA neurons. More precisely it was shown that the distribution of NK_3 receptor-like immunoreactivity neurons in rats completely overlaps that of tyrosine hydroxylase-like immunoreactive neurons in A8, A9 and A10 regions, suggesting a physiological modulation of dopaminergic neurons by tachykinins in these regions (Chen et al., 1998; Lessard et al., 2009). In line with this idea are electrophysiological studies in rats, which showed that NK_3 receptors mediate the principal excitatory effects of exogenously applied senktide on a subpopulation of dopamine-sensitive neurons in the ventral tegmental area and in the substantia nigra (Keegan et al., 1992; Nalivaiko et al., 1997; Overton et al., 1992; Seabrook et al., 1995). In primary cultures of gerbil mesencephalon, NK_3 receptor stimulation induced enhancement of spontaneous DA release and intracellular

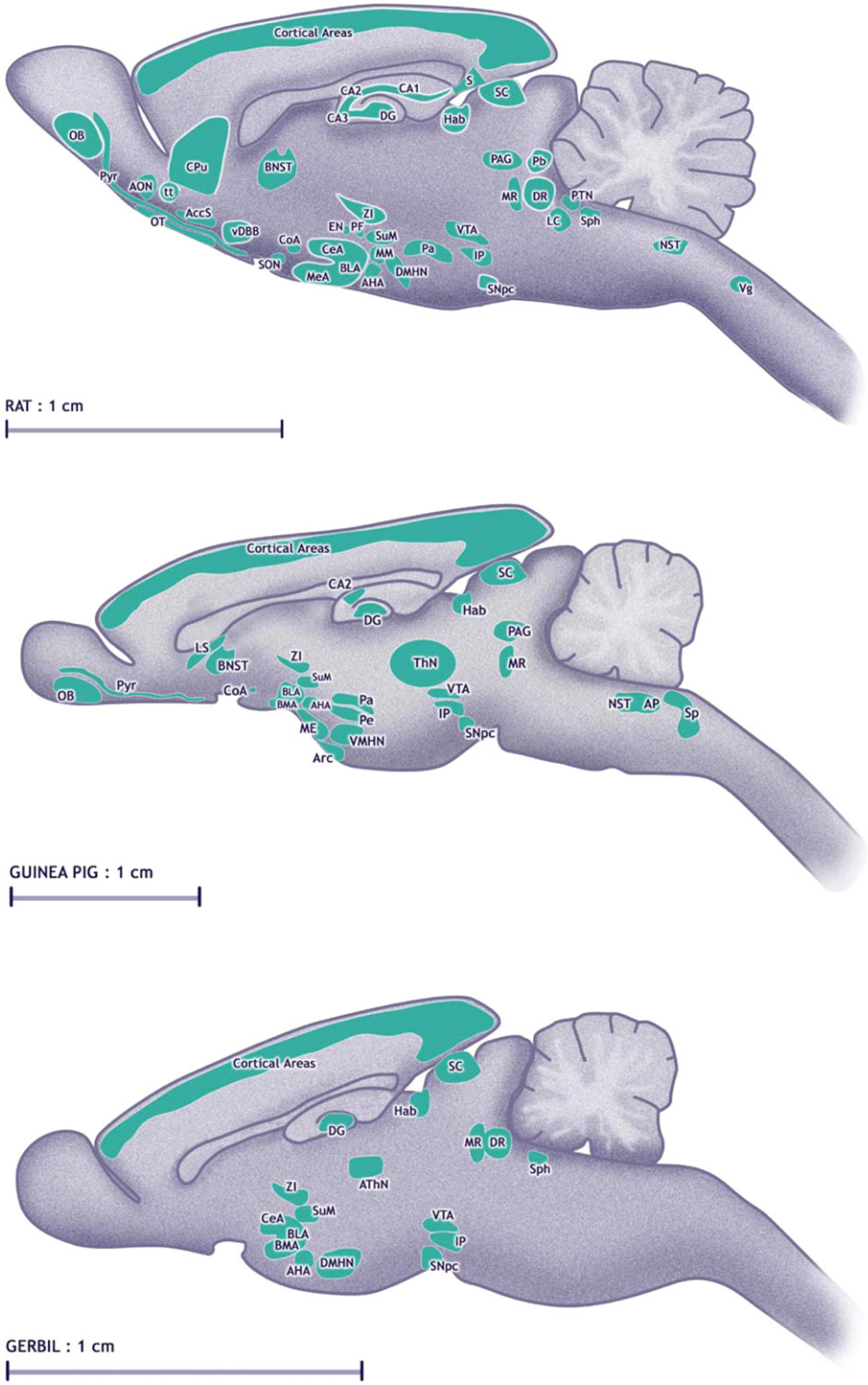

Fig. 1. Comparison of the distribution of the NK_3 receptor protein or mRNAs encoding NK_3 receptor in the rat, guinea pig and gerbil brain. Acc = accumbens nucleus, AccS = anterior cingulate cortex; AHA = anterior hypothalamic area; AP = area postrema, AON = anterior olfactory nucleus; AP = anteroposterior axis; Arc = arcuate nucleus; aThN = anterior thalamic nucleus, BLA = basolateral amygdala, BNST = bed nucleus of the stria terminalis, CA1 = hippocampal field CA1, CA2 = hippocampal field CA2, CA3 = hippocampal field CA3, CeA = central amygdala, CoA = cortical amygdaloid nucleus, CPu = caudate putamen; DG = dentate gyrus, DMHN = dorso medial hypothalamus nucleus; DR = dorsal raphe; EN = entorhinal cortex; Hab = medial habenula, IP = interpeduncular nucleus; LC = locus coeruleus; LS = lateral septum, ME = median eminence; MeA = median amygdala, MM = medial mammillary nucleus, MR = median raphe; NST = nucleus of the solitary tract, OB = olfactory bulb; OT = olfactory tubercle, Pa = paraventricular hypothalamic nucleus, PAG = periaqueductal gray; Pe = periventricular hypothalamic nucleus, PF = parafascicular thalamic nucleus; Pb = parabrachial nucleus; PTN = paratrigeminal nucleus; Pyr = pyriform; S = subiculum; SC = superior colliculus; SNpc = substantia nigra pars compacta; SON = supraoptic nucleus, Sp = stratum pyramidal; Sph = sphenoid nucleus; SuM = supramammillary nucleus; ThN = thalamus nuclei; tt = taenia tecta; vDBB = nucleus of the ventrical limb of the diagonal band; Vg = vagus nerve; VTA = ventral tegmental area; ZI = zone incerta.

Ca^{2+} mobilization in dopaminergic neurons (Alonso et al., 1996). An in vivo microdialysis study in guinea pigs demonstrated that infusions of senktide in the substantia nigra pars compacta or the ventral tegmental area increased the extracellular DA content in target areas, such as the striatum, the nucleus accumbens and the prefrontal cortex (Marco et al., 1998). These findings are substantiated by results from ex vivo

Table 1
Relative affinity of non-peptide NK_3 receptor antagonists to membranes of CHO cells expressing the human tachykinin receptors.

	K_i (nM)			
	hNK_3	hNK_1	hNK_2	
Osanetant	0.21 ± 0.03	>100,000	20.4 ± 5.7	(Emonds-Alt et al., 1995)
Talnetant	1.0 ± 0.1	>100,000	144 ± 22	(Sarau et al., 1997)
SB222200	4.4	>100,000	250	(Sarau et al., 2000)
SB235375	2.2 ± 0.3	>100,000	209 ± 14	(Hay et al., 2002)
SSR146977	0.26 ± 0.03	78 ± 2	19.3 ± 0.8	(Emonds-Alt et al., 2002)
GSK-256471 (pK_i)	8.9 ± 0.1	5.2 ± 0.1	7.3 ± 0.1	(Dawson et al., 2010)

Values are means ± SEM. Radioligands: [^{125}I]-iodohistidyl-[MePhe^7] neurokinin B (osanetant and SSR146977) or [^{125}I]-[MePhe^7] neurokinin B (talnetant, SB222200 and SB235375) for NK_3 receptors; [^{3}H]-substance P for NK_1 receptors, except SSR146977 for which [^{125}I]-Bolton-Hunter substance P was used; [^{3}H]-neurokinin A for NK_2 receptors, except SSR146977 for which [^{125}I]-iodohistidyl-neurokinin A was used.

biochemical studies in rats, which showed that application of NK_3 receptor agonists in the substantia nigra elevated levels of DOPAC and the DOPAC/DA ratio in the striatum, indicating increased dopaminergic metabolism and turnover (Bannon et al., 1995; Humpel et al., 1991; Humpel & Saria, 1993). Finally, behavioral studies demonstrated that administration of senktide into the ventral tegmental area and the substantia nigra produced behavioral effects reminiscent of dopaminergic activation, such as stimulation of locomotor activity, rearing, sniffing, yawning and chewing (Elliott et al., 1991; Liminga et al., 1991; Stoessl et al., 1991). Together, these findings that NK_3 receptor activation potentiates DA function in the midbrain have led to the idea that NK_3 receptor antagonists may be useful for the treatment of schizophrenia.

As indicated above, osanetant has been shown to prevent overactivity of the dopaminergic system elicited by senktide infusion in regions containing DA cell bodies (Marco et al., 1998; Nalivaiko et al., 1997). These findings were extended by an in vivo study in anesthetized guinea pigs that demonstrated that osanetant, which was totally inactive per se, dose-dependently prevented the increase in the spontaneously active (population response) DA cells in the A9 and A10 areas caused by acute administration of haloperidol (Gueudet et al., 1999). Similar effects were observed with SSR146977 (Emonds-Alt et al., 2002). The antagonistic effects of osanetant were also observed on the depolarization block-related decrease of ventral tegmental area cells population response evoked by repeated administration (22 days) of haloperidol. Moreover, the NK_3 receptor antagonist blocked activation of A10 neurons by the neurotensin receptor antagonist SR142948. The authors concluded that blockade of NK_3 receptors by osanetant seems to restore normal activity in cells whose levels of excitability have been driven far from baseline (Gueudet et al., 1999). More recent studies have demonstrated that the administration of NK_3 receptor antagonists stimulates cortical DA release, suggesting that they may counteract hypofrontality of patients with schizophrenia (de la Flor & Dawson, 2009). However, the situation is far from being clear. As mentioned above there are data suggesting that direct activation of NK_3 receptors also resulted in an increase in extracellular levels of DA in cortical structures. It was speculated that blockade of tonically active NK_3 receptors located on GABAergic neurons that are controlling the excitability of cortical neurons may lead to an increased DA efflux in cerebral cortex (de la Flor & Dawson, 2009).

Very few studies have investigated the behavioral effects of NK_3 receptor antagonists in animal models that are predictive of antipsychotic activity. Man et al. (2000) have used the prepulse inhibition (PPI) of the acoustic startle reflex in gerbils to examine potential antipsychotic properties of osanetant. PPI is reduced in schizophrenic patients and this can be modeled in animals by the administration of psychotomimetic drugs such as apomorphine. Results showed that the NK_3 receptor antagonist reversed apomorphine-induced deficit in PPI, an effect that was comparable to that obtained with the atypical antipsychotic risperidone. Antipsychotics selectively disrupt relatively weak responses maintained by conditioned stimuli as measured by conditioned avoidance paradigms in rodents (Van der Heyden & Bradford, 1988). When osanetant was tested in this procedure using guinea pigs as subjects, it blocked conditioned avoidance response, suggesting antipsychotic-like effects (unpublished data).

Several NK_3 receptor antagonists have been evaluated in patients with schizophrenia (Table 2). Preliminary data in a special study protocol termed Metatrial has revealed that osanetant, which was well tolerated, had an antipsychotic efficacy profile similar to that of the classical antipsychotic haloperidol. Notably, the NK_3 receptor antagonist displayed a significant improvement in primary efficacy scores (the Clinical Global Impressions [CGI] scale, the Brief Psychiatric Rating Scale [BPRS] and the Positive and Negative Syndrome Scale [PANSS]) at week 6 of the trial (Meltzer et al., 2004). Based on these findings, a second phase IIb clinical trial with osanetant was initiated. Unfortunately, this second, larger trial failed to demonstrate any significant efficacy of osanetant in schizophrenic patients, a result which led to the discontinuation of the development of the drug in 2005 (http://www.sanofi.com). Several phase II trials of talnetant in schizophrenia were performed. An initial placebo-controlled study revealed that the drug reduced significantly PANSS score to a similar extent as the antipsychotic drug risperidone, an effect which could not be replicated in a second small clinical trial, although patients exhibited some improvement of their cognitive symptoms (Evangelista, 2005). A reformulated version of talnetant was investigated in another phase II, but no further details were available at the time of publication. Instead, talnetant has been discontinued for the treatment of schizophrenia. More recently, AstraZeneca presented findings of

Table 2
Clinical trials with selective NK_3 receptor antagonists in schizophrenic patients.

Compound	Dose	Study	Primary efficacy measures	Results	Reference
Osanetant	200 mg	Phase IIa, placebo-controlled trial vs. haloperidol (10 mg)	PANSS, BPRS, CGI	Improvement in all primary efficacy parameters	(Meltzer et al., 2004)
Osanetant	50, 100, 200 mg	Phase IIb, placebo-controlled trial vs. risperidone	PANSS, BPRS, CGI	Inactive on primary efficacy variables	http://www.sanofi.com
Talnetant	200 mg	Phase IIb, placebo-controlled trial vs. risperidone (3 to 6 mg)	PANSS	Improvement in PANSS score	(Evangelista, 2005)
Talnetant	200, 600 mg	Phase IIa, placebo-controlled trial	PANSS	Inactive on primary efficacy variable	(Evangelista, 2005)
Talnetant	200, 400, 600 mg	Phase IIa, placebo-controlled trial vs. risperidone (1–3 mg)	PANSS	?	http://clinicaltrials.gov
AZD-2624	40 mg	Phase IIa, placebo-controlled trial vs. olanzapine (15 mg)	PANSS	Inactive on primary efficacy variable	(Simonsen et al., 2010)

BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions, PANSS = Positive and Negative Syndrome Scale.

another NK_3 receptor antagonist, AZD-2624, which revealed to be inactive in a phase IIa trial for schizophrenia (Simonsen et al., 2010).

3.2. Anxiety disorders

There is strong evidence that anxiety behaviors can be modulated by manipulations of central NK_1 or NK_2 mechanisms (Griebel, 1999; Griebel et al., 2001; Rupniak et al., 2001). The role of NK_3 receptors in the modulation of experimental anxiety has been much less investigated. However, the neuroanatomical distribution of NK_3 receptors suggests a potential role of this receptor in the control of emotional processes. NK_3 receptors are found in limbic structures, such as the amygdala and the hippocampus, areas traditionally implicated in the modulation of fear and anxiety. Moreover, NK_3 receptors are located in the dorsal raphe nucleus, a structure that has shown high sensitivity to a variety of anxiolytics, including serotonergic (5-HT) and GABAergic-modulating agents (Griebel, 1995).

Studies in animals have demonstrated a relationship between alterations in noradrenergic brain system function and behaviors associated with stress and anxiety (Bremner et al., 1996a, 1996b; Koob, 1999). The majority of noradrenergic cell bodies in the brain are located in the locus coeruleus, with projections throughout the cerebral cortex and multiple subcortical areas. The neuroanatomy of the afferent and efferent inputs to the locus coeruleus is suggestive of the role it may play in the stress response. Stress exposure is associated with an increase in firing of the locus coeruleus and with associated increased release of norepinephrine in brain regions which receive noradrenergic innervation. Similar to stress, the NK_3 receptor agonist senktide increased the firing rate of noradrenergic neurons in the locus coeruleus (Jung et al., 1996) and produced a dramatic increase in the release of norepinephrine in the prefrontal cortex of guinea pigs (Bert et al., 2002). Both these effects could be prevented by prior administration of the NK_3 receptor antagonists osanetant and SSR146977. Moreover, senktide was able to stimulate 5-HT transmission (Stoessl et al., 1987), which is known to play a crucial role in the control of anxiety (Griebel, 1995). Overall, this neuroanatomical and pharmacological information suggests that the blockade of central NK_3 receptors may attenuate stress-related behaviors.

Several studies have investigated the behavioral effects of NK_3 receptor ligands in animal models of anxiety (Table 3). Surprisingly, senktide was found to display anxiolytic-like effects (De Lima et al., 1995; Ribeiro et al., 1999; Ribeiro & DeLima, 1998) in some of these studies, whereas others have reported a lack of activity of NK_3 receptor agonists (Ribeiro & De Lima, 2002; Ribeiro & DeLima, 1998). Even more intriguing is the finding that the peptide NK_3 receptor antagonist [Trp^7β-Ala^8]$NKA_{(4–10)}$ produced an anxiogenic-like profile (Ribeiro et al., 1999). The reasons for these unexpected effects are unclear, but it is important to note that in all these studies mice were used as subjects. As indicated above, the NK_3 receptor is particularly remarkable for its pharmacological heterogeneity, an idea that is substantiated by the observation that the guinea pig and gerbil NK_3 receptors exhibit a similar pharmacological profile to the human NK_3 receptor, while that of the rat is somewhat different than the human NK_3 receptor. Information on the NK_3 receptor and its pharmacology in the mouse is lacking, thus precluding interspecies generalization of the behavioral effects of NK_3 receptor ligands in mice. A few studies have used gerbils to investigate the potential effects of osanetant and SSR146977 in models of anxiety (Table 3). Results revealed that while osanetant was inactive in the light/dark test, the marble-burying paradigm and on stress-induced hyperthermia, it increased the number of punished crossings in the four-plate test and the time spent in social interaction by pairs of male gerbils, effects that are indicative of an anxiolytic-like action in these procedures (Boissier et al., 1968; File et al., 2001). Similar effects were obtained with SSR146977 in the social interaction test. However, taken as a whole these findings do not demonstrate convincingly that NK_3 receptor antagonists may be of therapeutic utility for anxiety disorders. Consistent with this idea are findings from a clinical trial with osanetant in outpatients suffering from panic disorder, which showed that the compound was not significantly different from placebo (Kronenberg et al., 2005).

3.3. Depressive disorders

Although NK_3 receptors are highly expressed in brain regions that are involved in the regulation of affective disorders (see paragraph above) and are found in close association with 5-HT containing neurons that are targeted by the currently used antidepressant drugs, there is a deficiency of information on the potential of NK_3 receptor ligands in depression. Moreover, the available data in laboratory animals are equivocal regarding the antidepressant potential of NK_3 receptor ligands. One study has demonstrated that the NK_3 receptor agonist aminosenktide displayed antidepressant-like activity in the forced-swim test, a widely used model of depression, when a mouse line with overactivity of the opioid system was used (Panocka et al., 2001). It is noteworthy that these effects were abolished by the opioid receptor antagonist naloxone, suggesting that the antidepressant-like action of the NK_3 receptor agonist is dependent upon the activity of the endogenous opioid system.

The finding of an antidepressant-like profile after NK_3 receptor stimulation does not fit well with a recent observation that osanetant produced antidepressant-like activity in the forced-swim test in rats, an effect which was comparable to that of amitriptyline and desipramine, two well-established antidepressants (Dableh et al., 2002). Moreover, osanetant was found active in the stress-induced tonic

Table 3
The effects of NK_3 receptor-modulating drugs in anxiety models.

Drug	Action	Model	Species	Doses	Route, min	Effect	Reference
Neurokinin B	Endogenous NK_3 ligand	Elevated plus-maze	Mice	1–500 pmol/2 μl	i.c.v., 5	o	(Ribeiro et al., 1999)
Senktide	NK_3 agonist	Elevated plus-maze	Mice	10 pmol	i.c.v., 5	+	(Ribeiro & DeLima, 1998)
Senktide		Elevated plus-maze	Mice	100 pmol/2 μl	i.c.v., 0	o	(Ribeiro & De Lima, 2002)
Senktide		Elevated plus-maze	Mice	0.1–500 pmol/5 μl	i.c.v., 5	+	(De Lima et al., 1995)
Senktide		Elevated plus-maze	Mice	100–500 pmol/2 μl	i.c.v., 5	+	(Ribeiro et al., 1999)
[Trp^7 β-Ala^8]$NKA_{(4–10)}$	NK_3 antagonist	Elevated plus-maze	Mice	100 pmol/2 μl	i.c.v., 0	o	(Ribeiro & De Lima, 2002)
[Trp^7 β-Ala^8]$NKA_{(4–10)}$		Elevated plus-maze	Mice	10 pmol/2 μl	i.c.v., 5	−	(Ribeiro et al., 1999)
[Trp^7β-Ala^8]$NKA_{(4–10)}$		Elevated plus-maze	Mice	100 pmol	i.c.v., 5	o	(Ribeiro & DeLima, 1998)
Osanetant	NK_3 antagonist	Light/dark box	Gerbils	1–10 mg/kg	ip, 30	o	Unpublished
Osanetant		Marble burying	Gerbils	3–10 mg/kg	ip, 30	o	Unpublished
Osanetant		Stress-induced hyperthermia	Gerbils	1–10 mg/kg	po, 60	o	Unpublished
Osanetant		Social interaction	Gerbils	1–30 mg/kg	po, 60	+	(Salome et al., 2006)
Osanetant		Elevated plus-maze	Mice	100 pmol	i.c.v., 5	o	(Ribeiro & DeLima, 1998)
Osanetant		Elevated plus-maze	Mice	1–500 pmol/2 μl	i.c.v., 5	o	(Ribeiro et al., 1999)
Osanetant		Four-plate	Gerbils	20	ip, 30	+	Unpublished
SSR146977	NK_3 antagonist	Social interaction	Gerbils	3–10 mg/kg	po, 60	+	Unpublished

+ produced anxiolytic-like effects; − produced anxiogenic-like effects; o was inactive.

immobility paradigm in gerbils, an experimental procedure which has proved to be sensitive to antidepressants only (Salome et al., 2006). The unexpected similarity in drug effects between NK_3 stimulation and blockade may be explained in part by the use of different species (mouse vs. rat, gerbils). Moreover, the fact that aminosenktide required high activity of the opioid system to produce antidepressant-like effects makes it difficult to draw firm conclusions on the antidepressant potential of NK_3 receptor activation. Based on the above-mentioned observations that NK_3 receptor stimulation triggers brain systems involved in the regulation of the stress response, antidepressant-like effects of NK_3 receptor antagonists would be more in accordance with prediction. However, two phase II studies evaluating the potential of 50, 100 and/or 200 mg osanetant in severe depression proved non-conclusive. After six weeks of treatment, no significant difference was observed between osanetant (50, 100 and 200 mg), fluoxetine (20 mg) and placebo (Simonsen et al., 2010).

3.4. Addiction

There are several lines of evidence suggesting that the NK_3 receptor may be involved in reward processes (for a review, see Massi et al., 2000). Massi and colleagues showed that central or peripheral infusions of the NK_3 receptor agonists aminosenktide and senktide exerted rewarding effects in rats in the place conditioning paradigm (Ciccocioppo et al., 1998), but inhibited ethanol intake in the genetically selected Sardinian alcohol-preferring rats (Ciccocioppo et al., 1994, 1995, 1997; Panocka et al., 1998; Perfumi et al., 1991). These latter effects were abolished by the peptide NK_3 receptor antagonist R820 when both the agonist and the antagonist were administered in the nucleus basalis magnocellularis (Ciccocioppo et al., 1997). To explain these effects, it was hypothesized that NK_3 receptor agonists reduce ethanol intake by substituting the rewarding properties of ethanol (Massi et al., 2000). More recently, it was demonstrated that NK_3 is associated with alcohol and cocaine dependence following the observation of polymorphisms in the NK_3 receptor-encoding gene, which was suggested to contribute to the variation in more severe alcohol dependent individuals and those who are also cocaine dependent (Foroud et al., 2008). Moreover, osanetant was found to block the behavioral effects of cocaine in marmosets (De Souza Silva et al., 2006). The mechanisms underlying the action of NK_3 receptor agonists on reward processes remain to be determined, but certainly involve neurotransmitter systems that are known to play a central role in reward, such as DA or opioids, which show strong interactions with the tachykinergic system, in particular the NK_3 receptor (Nwaneshiudu & Unterwald, 2009). To date, it is not known whether NK_3 receptor antagonists may influence reward processes.

4. Conclusion

The NK_3 receptor has been suggested many times to represent a promising new target for the treatment of several psychiatric disorders, with a focus on schizophrenia. This idea was based in great part on data from preclinical studies highlighting that NK_3 receptors have diverse modulatory roles on a number of key neurotransmitter systems involved in the pathophysiology of these CNS conditions, findings which have led to this target being progressed into the clinic. Unfortunately, taken as a whole, the available clinical findings with selective NK_3 receptor antagonists in psychiatric diseases, in particular schizophrenia, have not convincingly established that the blockade of this neuropeptide receptor may be sufficient to improve these conditions. It has been suggested that suboptimal pharmacokinetic characteristics of osanetant and talnetant, such as limited brain penetration, may account at least in part for their poor efficacy in clinical trials. However, at least in the case of talnetant, it was established that the drug penetrates the brain (Liem-Moolenaar et al., 2008). Alternatively, possible species differences in the physiology of the NK_3 system may be a factor. Perhaps, it is more reasonable to think that the selective blockade of the NK_3 receptor in the brain may not be sufficient to achieve significant therapeutic efficacy in psychiatric conditions such as schizophrenia or major depressive disorders and that these compounds may find some utility when combined with clinically effective drugs in order for example to reduce the dose-levels of these latter and, consequently, to limit some of their unwanted effects. Unfortunately, in part because of the abovementioned clinical failures, pharmaceutical companies have greatly reduced or abandoned research and development on this target and there is currently no selective NK_3 receptor antagonist in clinical development for a psychiatric condition, thus questioning the future of these drugs for CNS disorders. Today, only Roche seems to pursue some activities in the NK_3 field by developing dual NK_1/NK_3 receptor antagonists, which could have improved efficacy when compared to selective NK_3 receptor antagonists, notably against schizophrenia and mood disorders (Malherbe et al., 2011b).

Conflict of interest

The authors declare that there are no conflicts of interest.

References

Almeida, T. A., Rojo, J., Nieto, P. M., Pinto, F. M., Hernandez, M., Martin, J. D., et al. (2004). Tachykinins and tachykinin receptors: Structure and activity relationships. *Curr Med Chem 11*, 2045–2081.

Alonso, R., Fournier, M., Carayon, P., Petitpretre, G., Le Fur, G., & Soubrié, P. (1996). Evidence for modulation of dopamine-neuronal function by tachykinin NK3 receptor stimulation in gerbil mesencephalic cell cultures. *Eur J Neurosci 8*, 801–808.

Bannon, M. J., Brownschidle, L. A., Tian, Y., Whitty, C. J., Poosch, M. S., D'sa, C., et al. (1995). Neurokinin-3 receptors modulate dopamine cell function and alter the effects of 6-hydroxydopamine. *Brain Res 695*, 19–24.

Bert, L., Rodier, D., Bougault, I., Allouard, N., Le Fur, G., Soubrié, P., et al. (2002). Permissive role of neurokinin NK_3 receptors in NK_1 receptor-mediated activation of the locus coeruleus revealed by SR 142801. *Synapse 43*, 62–69.

Boissier, J. R., Simon, P., & Aron, C. (1968). A new method for the rapid screening of minor tranquilisers in mice. *Eur J Pharmacol 4*, 145–151.

Bonner, T. I., Affolter, H. U., Young, A. C., & Young, W. S., III (1987). A cDNA encoding the precursor of the rat neuropeptide, neurokinin B. *Brain Res 388*, 243–249.

Bremner, J. D., Krystal, J. H., Southwick, S. M., & Charney, D. S. (1996). Noradrenergic mechanisms in stress and anxiety. 1. Preclinical studies. *Synapse 23*, 28–38.

Bremner, J. D., Krystal, J. H., Southwick, S. M., & Charney, D. S. (1996). Noradrenergic mechanisms in stress and anxiety. 2. Clinical studies. *Synapse 23*, 39–51.

Buck, S. H., Helke, C. J., Burcher, E., Shults, C. W., & O'Donohue, T. L. (1986). Pharmacologic characterization and autoradiographic distribution of binding sites for iodinated tachykinins in the rat central nervous system. *Peptides 7*, 1109–1120.

Carpentier, C., & Baude, A. (1996). Immunocytochemical localisation of NK3 receptors in the dorsal vagal complex of rat. *Brain Res 734*, 327–331.

Carter, M. S., & Krause, J. E. (1990). Structure, expression, and some regulatory mechanisms of the rat preprotachykinin gene encoding substance P, neurokinin A, neuropeptide K, and neuropeptide gamma. *J Neurosci 10*, 2203–2214.

Chen, L. W., Guan, Z. L., & Ding, Y. Q. (1998). Mesencephalic dopaminergic neurons expressing neuromedin K receptor (NK3): A double immunocytochemical study in the rat. *Brain Res 780*, 150–154.

Ciccocioppo, R., Panocka, I., Polidori, C., de Caro, G., Regoli, D., & Massi, M. (1997). Stimulation of tachykinin NK-3 receptors in the nucleus basalis magnocellularis reduces alcohol intake in rats. *Peptides 18*, 1349–1355.

Ciccocioppo, R., Panocka, I., Polidori, C., Froldi, R., Angeletti, S., & Massi, M. (1998). Mechanism of action for reduction of ethanol intake in rats by the tachykinin NK-3 receptor agonist aminosenktide. *Pharmacol Biochem Behav 61*, 459–464.

Ciccocioppo, R., Panocka, I., Pompei, P., de Caro, G., & Massi, M. (1994). Selective agonists at NK3 tachykinin receptors inhibit alcohol intake in Sardinian alcohol-preferring rats. *Brain Res Bull 33*, 71–77.

Ciccocioppo, R., Panocka, I., Pompei, P., Polidori, C., de Caro, G., & Massi, M. (1995). Subcutaneous injections of the tachykinin senktide reduce alcohol intake in alcohol-preferring rats. *Peptides 16*, 533–537.

Dableh, L. J., Yashpal, K., Rochford, J., & Henry, J. L. (2002). *Therapeutic potential of NK-1, -2 and -3 receptor inhibition in an animal model of depression.* Program No 307 4 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience CD-ROM.

Dam, T. V., Escher, E., & Quirion, R. (1990). Visualization of neurokinin-3 receptor sites in rat brain using the highly selective ligand [^{3}H]senktide. *Brain Res 506*, 175–179.

Dawson, L. A., Langmead, C. J., Dada, A., Watson, J. M., Wu, Z., de la, F. R., et al. (2010). In vitro and in vivo comparison of two non-peptide tachykinin NK3 receptor antagonists: Improvements in efficacy achieved through enhanced brain penetration or altered pharmacological characteristics. *Eur J Pharmacol 627*, 106–114.

Dawson, L. A., & Smith, P. W. (2010). Therapeutic utility of NK3 receptor antagonists for the treatment of schizophrenia. *Curr Pharm Des 16*, 344–357.

de la Flor, R., & Dawson, L. A. (2009). Augmentation of antipsychotic-induced neurochemical changes by the NK3 receptor antagonist talnetant (SB-223412). *Neuropharmacology 56*, 342–349.
De Lima, T. C. M., Teixeira, R. M., Santos, A. R. S., Rae, G. A., & Calixto, J. B. (1995). Behavioral effects of intracerebroventricular injection of selective tachykinin agonists and antagonists. *Soc Neurosci Abstr 21*, 1696.
De Souza Silva, M. A., Mello, E. L., Jr., Muller, C. P., Jocham, G., Maior, R. S., Huston, J. P., et al. (2006). The tachykinin NK3 receptor antagonist SR142801 blocks the behavioral effects of cocaine in marmoset monkeys. *Eur J Pharmacol 536*, 269–278.
Ding, Y. Q., Shigemoto, R., Takada, M., Ohishi, H., Nakanishi, S., & Mizuno, N. (1996). Localization of the neuromedin K receptor (NK3) in the central nervous system of the rat. *J Comp Neurol 364*, 290–310.
Ebner, K., Sartori, S. B., & Singewald, N. (2009). Tachykinin receptors as therapeutic targets in stress-related disorders. *Curr Pharm Des 15*, 1647–1674.
Elliott, P. J., Mason, G. S., Stephens-Smith, M., & Hagan, R. M. (1991). Behavioural and biochemical responses following activation of midbrain dopamine pathways by receptor selective neurokinin agonists. *Neuropeptides 19*, 119–126.
Emonds-Alt, X., Bichon, D., Ducoux, J. P., Heaulme, M., Miloux, B., Poncelet, M., et al. (1995). SR 142801, the first potent non-peptide antagonist of the tachykinin NK3 receptor. *Life Sci 56*, L27–L32.
Emonds-Alt, X., Proietto, V., Steinberg, R., Advenier, C., Daoui, S., Naline, E., et al. (2002). Biochemical and pharmacological activities of SSR 146977, a new potent nonpeptide tachykinin NK3 receptor antagonist. *Can J Physiol Pharmacol 80*, 482–488.
Emonds-Alt, X., Vilain, P., Goulaouic, P., Proietto, V., Van Broek, D., Advenier, C., et al. (1992). A potent and selective non-peptide antagonist of the neurokinin A (NK_2) receptor. *Life Sci 50*, PL-101–PL-106.
Evangelista, S. (2005). Talnetant GlaxoSmithKline. *Curr Opin Investig Drugs 6*, 717–721.
File, S. E., Cheeta, S., & Akanezi, C. (2001). Diazepam and nicotine increase social interaction in gerbils: A test for anxiolytic action. *Brain Res 888*, 311–313.
Foroud, T., Wetherill, L. F., Kramer, J., Tischfield, J. A., Nurnberger, J. I., Jr., Schuckit, M. A., et al. (2008). The tachykinin receptor 3 is associated with alcohol and cocaine dependence. *Alcohol Clin Exp Res 32*, 1023–1030.
Griebel, G. (1995). 5-Hydroxytryptamine-interacting drugs in animal models of anxiety disorders: More than 30 years of research. *Pharmacol Ther 65*, 319–395.
Griebel, G. (1999). Is there a future for neuropeptide receptor ligands in the treatment of anxiety disorders? *Pharmacol Ther 82*, 1–61.
Griebel, G., Perrault, G., & Soubrie, P. (2001). Effects of SR48968, a selective non-peptide NK2 receptor antagonist on emotional processes in rodents. *Psychopharmacology 158*, 241–251.
Gueudet, C., Santucci, V., Soubrie, P., & Le Fur, G. (1999). Blockade of neurokinin3 receptors antagonizes drug-induced population response and depolarization block of midbrain dopamine neurons in guinea pigs. *Synapse 33*, 71–79.
Hay, D. W., Giardina, G. A., Griswold, D. E., Underwood, D. C., Kotzer, C. J., Bush, B., et al. (2002). Nonpeptide tachykinin receptor antagonists. III. SB 235375, a low central nervous system-penetrant, potent and selective neurokinin-3 receptor antagonist, inhibits citric acid-induced cough and airways hyper-reactivity in guinea pigs. *J Pharmacol Exp Ther 300*, 314–323.
Helke, C. J., Krause, J. E., Mantyh, P. W., Couture, R., & Bannon, M. J. (1990). Diversity in mammalian tachykinin peptidergic neurons: Multiple peptides, receptors, and regulatory mechanisms. *FASEB J 4*, 1606–1615.
Humpel, C., & Saria, A. (1993). Intranigral injection of selective neurokinin-1 and neurokinin-3 but not neurokinin-2 receptor agonists biphasically modulate striatal dopamine metabolism but not striatal preprotachykinin-A mRNA in the rat. *Neurosci Lett 157*, 223–226.
Humpel, C., Saria, A., & Regoli, D. (1991). Injection of tachykinins and selective neurokinin receptor ligands into the substantia nigra reticulata increases striatal dopamine and 5-hydroxytryptamine metabolism. *Eur J Pharmacol 195*, 107–114.
Juhl, K., Hansen, T., Kehler, J., Khanzhin, N. A., Norgaard, M. B., Ruhland, T., et al. (2011). Identification of a new series of non-peptidic NK_3 receptor antagonists. *Bioorg Med Chem Lett 21*, 1498–1501.
Jung, M., Michaud, J. C., Steinberg, R., Barnouin, M. C., Hayar, A., Mons, G., et al. (1996). Electrophysiological, behavioural and biochemical evidence for activation of brain noradrenergic systems following neurokinin NK3 receptor stimulation. *Neuroscience 74*, 403–414.
Keegan, K. D., Woodruff, G. N., & Pinnock, R. D. (1992). The selective NK3 receptor agonist senktide excites a subpopulation of dopamine-sensitive neurones in the rat substantia nigra pars compacta in vitro. *Br J Pharmacol 105*, 3–5.
Koob, G. F. (1999). Corticotropin-releasing factor, norepinephrine, and stress. *Biol Psychiatry 46*, 1167–1180.
Kronenberg, G., Berger, P., Tauber, R. F., Bandelow, B., Henkel, V., & Heuser, I. (2005). Randomized, double-blind study of SR142801 (Osanetant). A novel neurokinin-3 (NK3) receptor antagonist in panic disorder with pre- and posttreatment cholecystokinin tetrapeptide (CCK-4) challenges. *Pharmacopsychiatry 38*, 24–29.
Langlois, X., Wintmolders, C., te, R. P., Leysen, J. E., & Jurzak, M. (2001). Detailed distribution of neurokinin 3 receptors in the rat, guinea pig and gerbil brain: A comparative autoradiographic study. *Neuropharmacology 40*, 242–253.
Lessard, A., Savard, M., Gobeil, F., Jr., Pierce, J. P., & Pickel, V. M. (2009). The neurokinin-3 (NK3) and the neurokinin-1 (NK1) receptors are differentially targeted to mesocortical and mesolimbic projection neurons and to neuronal nuclei in the rat ventral tegmental area. *Synapse 63*, 484–501.
Liem-Moolenaar, M., Gray, F., de, V. S., Franson, K., Schoemaker, R., Schmitt, J., et al. (2008). Psychomotor and cognitive effects of a single oral dose of talnetant (SB223412) in healthy volunteers compared with placebo or haloperidol. *J Psychopharmacol*.
Liminga, U., Johansson, P. E., & Gunne, L. (1991). Intranigral tachykinin NK3 receptor agonist elicits oral movements in rats. *Pharmacol Biochem Behav 38*, 617–620.
Maggi, C. A. (1995). The mammalian tachykinin receptors. *Gen Pharmacol 26*, 911–944.
Malherbe, P., Ballard, T. M., & Ratni, H. (2011). Tachykinin neurokinin 3 receptor antagonists: A patent review (2005–2010). *Expert Opin Ther Pat 21*, 637–655.
Malherbe, P., Knoflach, F., Hernandez, M. C., Hoffmann, T., Schnider, P., Porter, R. H., et al. (2011). Characterization of RO4583298 as a novel potent, dual antagonist with *in vivo* activity at tachykinin NK_1 and NK_3 receptors. *Br J Pharmacol 162*, 929–946.
Man, J., Jurzak, M., & Stohr, T. (2000). The NK3 receptor antagonist SR142801 reverses apomorphine-induced deficits on prepulse inhibition in gerbils. *Behav Pharmacol 11*, 343.
Marco, N., Thirion, A., Mons, G., Bougault, I., Lefur, G., Soubrie, P., et al. (1998). Activation of dopaminergic and cholinergic neurotransmission by tachykinin NK_3 receptor stimulation: An in vivo microdialysis approach in guinea pig. *Neuropeptides 32*, 481–488.
Massi, M., Panocka, I., & de Caro, G. (2000). The psychopharmacology of tachykinin NK-3 receptors in laboratory animals. *Peptides 21*, 1597–1609.
Medhurst, A. D., Parsons, A. A., Roberts, J. C., & Hay, D. W. (1997). Characterization of NK3 receptors in rabbit isolated iris sphincter muscle. *Br J Pharmacol 120*, 93–101.
Meltzer, H. Y., Arvanitis, L., Bauer, D., & Rein, W. (2004). Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. *Am J Psychiatry 161*, 975–984.
Munoz, M., & Covenas, R. (2011). NK-1 receptor antagonists: A new paradigm in pharmacological therapy. *Curr Med Chem 18*, 1820–1831.
Mussap, C. J., & Burcher, E. (1990). [^{125}I]-Bolton-Hunter scyliorhinin II: A novel, selective radioligand for the tachykinin NK3 receptor in rat brain. *Peptides 11*, 827–836.
Nalivaiko, E., Michaud, J. C., Soubrie, P., Le Fur, G., & Feltz, P. (1997). Tachykinin neurokinin-1 and neurokinin-3 receptor-mediated responses in guinea-pig substantia nigra: An in vitro electrophysiological study. *Neuroscience 78*, 745–757.
Nguyen, Q. T., Jukic, D., Chretien, L., Gobeil, F., Boussougou, M., & Regoli, D. (1994). Two NK-3 receptor subtypes: Demonstration by biological and binding assays. *Neuropeptides 27*, 157–161.
Nordquist, R. E., Ballard, T. M., Algeyer, B., Pauly-Evers, M., Ozmen, L., & Spooren, W. (2010). Pharmacological characterization of senktide-induced tail whips. *Neuropharmacology 58*, 259–267.
Nwaneshiudu, C. A., & Unterwald, E. M. (2009). Blockade of neurokinin-3 receptors modulates dopamine-mediated behavioral hyperactivity. *Neuropharmacology 57*, 295–301.
Otsuka, M., & Yoshioka, K. (1993). Neurotransmitter functions of mammalian tachykinins. *Physiol Rev 73*, 229–308.
Oury-Donat, F., Carayon, P., Thurneyssen, O., Pailhon, V., Emonds-Alt, X., Soubrie, P., et al. (1995). Functional characterization of the nonpeptide neurokinin3 (NK3) receptor antagonist, SR142801 on the human NK3 receptor expressed in Chinese hamster ovary cells. *J Pharmacol Exp Ther 274*, 148–154.
Overton, P., Elliott, P. J., Hagan, R. M., & Clark, D. (1992). Neurokinin agonists differentially affect A9 and A10 dopamine cells in the rat. *Eur J Pharmacol 213*, 165–166.
Panocka, I., Ciccocioppo, R., Polidori, C., Angeletti, S., de Caro, G., & Massi, M. (1998). Sensitivity of brain sites to the inhibitory effect on alcohol intake of the tachykinin aminosenktide. *Peptides 19*, 897–905.
Panocka, I., Massi, M., Lapo, I., Swiderski, T., Kowalczyk, M., & Sadowski, B. (2001). Antidepressant-type effect of the NK3 tachykinin receptor agonist aminosenktide in mouse lines differing in endogenous opioid system activity. *Peptides 22*, 1037–1042.
Perfumi, M., Polidori, C., Pompei, P. L., de Caro, G., & Massi, M. (1991). The tachykinin NH2-senktide inhibits alcohol intake in alcohol- preferring rats. *Pharmacol Biochem Behav 38*, 881–887.
Pinto, F. M., Almeida, T. A., Hernandez, M., Devillier, P., Advenier, C., & Candenas, M. L. (2004). mRNA expression of tachykinins and tachykinin receptors in different human tissues. *Eur J Pharmacol 494*, 233–239.
Quartara, L., Altamura, M., Evangelista, S., & Maggi, C. A. (2009). Tachykinin receptor antagonists in clinical trials. *Expert Opin Investig Drugs 18*, 1843–1864.
Ribeiro, R. L., & De Lima, T. C. M. (2002). Participation of GABA(A) receptors in the modulation of experimental anxiety by tachykinin agonists and antagonists in mice. *Prog Neuropsychopharmacol Biol Psychiatry 26*, 861–869.
Ribeiro, S. J., & DeLima, T. C. M. (1998). Naloxone-induced changes in tachykinin NK3 receptor modulation of experimental anxiety in mice. *Neurosci Lett 258*, 155–158.
Ribeiro, S. J., Teixeira, R. M., Calixto, J. B., & DeLima, T. C. M. (1999). Tachykinin NK3 receptor involvement in anxiety. *Neuropeptides 33*, 181–188.
Rupniak, N. M. J., Carlson, E. J., Webb, J. K., Harrison, T., Porsolt, R. D., Roux, S., et al. (2001). Comparison of the phenotype of NK1R−/− mice with pharmacological blockade of the substance P (NK1) receptor in assays for antidepressant and anxiolytic drugs. *Behav Pharmacol 12*, 497–508.
Saffroy, M., Torrens, Y., Glowinski, J., & Beaujouan, J. C. (2003). Autoradiographic distribution of tachykinin NK2 binding sites in the rat brain: Comparison with NK1 and NK3 binding sites. *Neuroscience 116*, 761–773.
Salome, N., Stemmelin, J., Cohen, C., & Griebel, G. (2006). Selective blockade of NK2 or NK3 receptors produces anxiolytic- and antidepressant-like effects in gerbils. *Pharmacol Biochem Behav 83*, 533–539.
Sarau, H. M., Griswold, D. E., Bush, B., Potts, W., Sandhu, P., Lundberg, D., et al. (2000). Nonpeptide tachykinin receptor antagonists. II. Pharmacological and pharmacokinetic profile of SB-222200, a central nervous system penetrant, potent and selective NK-3 receptor antagonist. *J Pharmacol Exp Ther 295*, 373–381.
Sarau, H. M., Griswold, D. E., Potts, W., Foley, J. J., Schmidt, D. B., Webb, E. F., et al. (1997). Nonpeptide tachykinin receptor antagonists: I. Pharmacological and pharmacokinetic characterization of SB 223412, a novel, potent and selective neurokinin-3 receptor antagonist. *J Pharmacol Exp Ther 281*, 1303–1311.
Seabrook, G. R., Bowery, B. J., & Hill, R. G. (1995). Pharmacology of tachykinin receptors on neurones in the ventral tegmental area of rat brain slices. *Eur J Pharmacol 273*, 113–119.

Shughrue, P. J., Lane, M. V., & Merchenthaler, I. (1996). In situ hybridization analysis of the distribution of neurokinin-3 mRNA in the rat central nervous system. *J Comp Neurol 372*, 395–414.

Simonsen, K. B., Juhl, K., Steiniger-Brach, B., & Nielsen, S. M. (2010). Novel NK_3 receptor antagonists for the treatment of schizophrenia and other CNS indications. *Curr Opin Drug Discov Devel 13*, 379–388.

Smith, P. W., Wyman, P. A., Lovell, P., Goodacre, C., Serafinowska, H. T., Vong, A., et al. (2009). New quinoline NK3 receptor antagonists with CNS activity. *Bioorg Med Chem Lett 19*, 837–840.

Spooren, W., Riemer, C., & Meltzer, H. (2005). Opinion: NK3 receptor antagonists: The next generation of antipsychotics? *Nat Rev Drug Discov 4*, 967–975.

Stoessl, A. J., Dourish, C. T., Young, S. C., Williams, B. J., Iversen, S. D., & Iversen, L. L. (1987). Senktide, a selective neurokinin B-like agonist, elicits serotonin-mediated behaviour following intracisternal administration in the mouse. *Neurosci Lett 80*, 321–326.

Stoessl, A. J., & Hill, D. R. (1990). Autoradiographic visualization of NK-3 tachykinin binding sites in the rat brain, utilizing [^{3}H]senktide. *Brain Res 534*, 1–7.

Stoessl, A. J., Szczutkowski, E., Glenn, B., & Watson, I. (1991). Behavioural effects of selective tachykinin agonists in midbrain dopamine regions. *Brain Res 565*, 254–262.

Suman-Chauhan, N., Grimson, P., Guard, S., Madden, Z., Chung, F. Z., Watling, K., et al. (1994). Characterisation of [125I][MePhe7]neurokinin B binding to tachykinin NK3 receptors: Evidence for interspecies variance. *Eur J Pharmacol 269*, 65–72.

Sundqvist, M., Kristensson, E., Adolfsson, R., Leffler, A., Ahlstedt, I., Engberg, S., et al. (2007). Senktide-induced gerbil foot tapping behaviour is blocked by selective tachykinin NK1 and NK3 receptor antagonists. *Eur J Pharmacol 577*, 78–86.

Van der Heyden, J. A., & Bradford, L. D. (1988). A rapidly acquired one-way conditioned avoidance procedure in rats as a primary screening test for antipsychotics: Influence of shock intensity on avoidance performance. *Behav Brain Res 31*, 61–67.

Yip, J., & Chahl, L. A. (2001). Localization of NK1 and NK3 receptors in guinea-pig brain. *Regul Pept 98*, 55–62.