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

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A B S T R A C T

Selective non-peptide antagonists for the neurokinin 3 (NK3) receptor first became available about twenty years ago. Although the understanding of the role of the NK3 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 NK3 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 NK3 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 NK3 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.

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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-NH₂, 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, vasodilation, secretion, activation of the immune system, pain transmission and neurogenic inflammation, and are implicated in a broad range of CNS disorders. 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 NK₁ receptor, while NKA and NKB are naturally occurring agonists for the NK₂ and NK₃ 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.

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The purpose of this article is to provide a critical overview on the therapeutic potential of NK3 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 NK3 receptor antagonist. For an overview of the therapeutic potential of NK3 and NK2 receptor antagonists, the reader is directed towards recently published reviews (Ehner et al., 2009; Munoz & Covena, 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 NK3 receptors are highly expressed in both the CNS and peripheral tissues, and NK2 receptors are characterized by a predominant expression in the periphery, NK3 receptors are found primarily in the CNS. The distribution of NK3 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 NK3 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 NK3 receptors (Fig. 1). For example, the guinea pig was the only species where NK3 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 NK3 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 NK3 receptors. This idea is strengthened by the observation that the rat NK3 receptor exhibits a different pharmacological profile than the human NK3 receptor, while that of the guinea pig and, to a lesser extent, the gerbil, is similar to the human NK3 receptor (Nguyen et al., 1994; Suman-Chauhan et al., 1994). Moreover, NK3 receptor antagonists generally have a higher affinity for the human, the gerbil and the guinea pig than for the rat NK3 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 NK3 receptor antagonist described in the literature (Emonds-Alt et al., 1995). The compound derived from chemical modifications of another dichlorophenylalkylpiperidine, the NK2 receptor antagonist saredusted (SR48968) (Emonds-Alt et al., 1992). Osanetant potently inhibited the binding of $[^{125}]$Iiodohistidyl-2-MePhe$^3$NKB to NK3 receptors from guinea pig and gerbil brain cortex ($K_i=0.11$ and 0.42 nM, respectively) and to cloned human NK3 receptors expressed in CHO cells ($K_i=0.21$ nM), but was less active on NK3 receptors from rat brain cortex as indicated by $[^{125}]$Ileolecin binding ($K_i=15$ nM) (Oury-Donat et al., 1995). Potent antagonist activity of osanetant at the NK3 receptor was demonstrated by its ability to inhibit acetylcholine release following activation of the guinea pig ileum NK3 receptor (Emonds-Alt et al., 1995) and the contractile response of rabbit iris sphincter muscle to the NK3 receptor agonist senktide (Medhurst et al., 1997). In CHO cells expressing human NK3 receptors, osanetant antagonized increases in inositol monophosphate formation, arachidonic acid release, cAMP accumulation and intracellular Ca$^{2+}$ concentrations induced by selective NK3 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; Naivalaiko et al., 1997). In vivo microdialysis experiments in guinea pigs showed that the NK3 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 stereosepecific as the inactive (S)-enantiomer, SR142806, was approximately 100-fold less effective than osanetant in inhibiting NK3 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 NK3 receptor. As of today there are more than 80 patent applications disclosing compounds claimed as NK3 receptor antagonists with a rich structural diversity (for further details, see Dawson & Smith, 2010; Juul et al., 2011; Malherbe et al., 2011a; Simonsen et al., 2010). Among the most investigated compounds are talnetant (formerly SB222412) (Sarau et al., 1997), SR146977 (Emonds-Alt et al., 2002), GSK-256471 (Smith et al., 2009), SB2222200 (Sarau et al., 2000) and SB235375 (Hay et al., 2002). They all showed high selectivity for NK3 versus NK1 and NK2 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 NK3 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 hNK3 receptor. Peripheral administration of talnetant, GSK256471, SR146977 and SB2222200, but not SB235375 inhibited stereotopies 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., 2002; 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 NK3 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). NK3 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 NK3 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 NK3 receptors mediate the principal excitatory effects of exogenously applied senktide on a subpopulation of dopaminergic-sensitive neurones in the ventral tegmental area and in the substantia nigra (Keegan et al., 1992; Naivalaiko et al., 1997; Overton et al., 1992; Seabrook et al., 1995). In primary cultures of gerbil mesencephalon, NK3 receptor stimulation induced enhancement of spontaneous DA release and intracellular...
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

Fig. 1. Comparison of the distribution of the NK3 receptor protein or mRNAs encoding NK3 receptor in the rat, guinea pig and gerbil brain. Acc = accumbens nucleus, AccS = anterior cingulate cortex; AH = anterior hypothalamic area; AP = area postrema; AGN = 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; CoA = central amygdala; COp = cortical amygdaloid nucleus; Cun = caudate putamen; DG = dentate gyrus; DMH = diencephalic nucleus; DR = dorsal raphe; EN = entorhinal cortex; Hab = habenular nucleus; IP = interpeduncular nucleus; LC = locus coeruleus; LME = lateral medullary 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; Ph = parabrachial nucleus; PN = paraventricular nucleus; Pyr = pyriform; S = subiculum; Sc = superior colliculus; SN = substantia nigra; SOr = supraoptic nucleus; Sp = stratum pyramidale; Sph = sphenoid nucleus; SuM = supramammillary nucleus; ThN = thalamus; tt = taenia tecta; vDBB = nucleus of the ventral limb of the diagonal band; vG = vagus nerve; VT = ventral tegmental area; ZI = zona incerta.
Moreover, the NK3 receptor antagonist blocked activation of A10 neuron block-related decrease of ventral tegmental area cells population by acute administration of haloperidol (Gueudet et al., 1999). Similar active (population response) DA cells in the A9 and A10 areas caused effects were observed with SSR146977 (Emonds-Alt et al., 2002). The administration of senktide into the ventral tegmental area and the substantia nigra produced behavioral effects reminiscent of dopaminergic properties. Together, these findings that NK3 receptor activation potentiates DA function in the midbrain have led to the idea that NK3 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 senkide 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 NK3 receptor antagonist blocked activation of A10 neurons by the neurotensin receptor antagonist SR142948. The authors concluded that blockade of NK3 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 NK3 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 NK3 receptors also resulted in an increase in extracellular levels of DA in cortical structures. It was speculated that blockade of tonically active NK3 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).

Several studies have investigated the behavioral effects of NK3 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 NK3 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 NK3 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 NK3 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 Ib 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 1

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>hNK3</th>
<th>hNK1</th>
<th>hNK2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK-256471 (pKi)</td>
<td>8.9±0.1</td>
<td>5.2±0.1</td>
<td>7.3±0.1</td>
</tr>
<tr>
<td>Talnetant</td>
<td>2.2±0.3</td>
<td>&gt;100,000</td>
<td>209±14</td>
</tr>
<tr>
<td>SSR146977</td>
<td>0.26±0.03</td>
<td>73±2</td>
<td>19.3±0.8</td>
</tr>
<tr>
<td>SB235375</td>
<td>4.4</td>
<td>&gt;100,000</td>
<td>250</td>
</tr>
<tr>
<td>SSR222200</td>
<td>1.0±0.1</td>
<td>&gt;100,000</td>
<td>144±22</td>
</tr>
</tbody>
</table>

Values are means±SEM. Radioligands: [125I]-iodohistidyl-[MePhe7]neurokinin B (osanetant and SSR146977) or [125I]-[MePhe7]neurokinin B (talnetant, SSR222200 and SB235375) for NK3 receptors; [3H]-substance P for NK1 receptors, except SSR146977 for which [3H]-bolton-Hunter substance P was used; [3H]-neurokinin A for NK2 receptors, except SSR146977 for which [3H]-iodo[3H]substance P was used.

### Table 2

Clinical trials with selective NK3 receptor antagonists in schizophrenic patients.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Study</th>
<th>Primary efficacy measures</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osanetant</td>
<td>200 mg</td>
<td>Phase Ila, placebo-controlled trial vs. haloperidol (10 mg)</td>
<td>PANSS, BPRS, CGI</td>
<td>Improvement in all primary efficacy parameters</td>
<td>(Meltzer et al., 2004)</td>
</tr>
<tr>
<td>Osanetant</td>
<td>50, 100, 200 mg</td>
<td>Phase Ib, placebo-controlled trial vs. risperidone</td>
<td>PANSS, BPRS, CGI</td>
<td>Inactive on primary efficacy variables</td>
<td><a href="http://www.sano%EF%AC%81.com">http://www.sanoﬁ.com</a></td>
</tr>
<tr>
<td>Talnetant</td>
<td>200 mg</td>
<td>Phase Iib, placebo-controlled trial vs. risperidone (3 to 6 mg)</td>
<td>PANSS</td>
<td>Improvement in PANSS score</td>
<td>(Evangelista, 2005)</td>
</tr>
<tr>
<td>Talnetant</td>
<td>200, 600 mg</td>
<td>Phase Ila, placebo-controlled trial</td>
<td>PANSS</td>
<td>Inactive on primary efficacy variable</td>
<td>(Evangelista, 2005)</td>
</tr>
<tr>
<td>Talnetant</td>
<td>200, 400, 600 mg</td>
<td>Phase Ila, placebo-controlled trial vs. risperidone (1–3 mg)</td>
<td>PANSS</td>
<td>?</td>
<td><a href="http://clinicaltrials.gov">http://clinicaltrials.gov</a></td>
</tr>
<tr>
<td>AZD-2624</td>
<td>40 mg</td>
<td>Phase Ila, placebo-controlled trial vs. olanzapine (15 mg)</td>
<td>PANSS</td>
<td>Inactive on primary efficacy variable</td>
<td>(Simonsen et al., 2010)</td>
</tr>
</tbody>
</table>

BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions, PANSS = Positive and Negative Syndrome Scale.
another NK3 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 NK3, or NK3, mechanisms (Griebel, 1999; Griebel et al., 2001; Rupniak et al., 2001). The role of NK3 receptors in the modulation of experimental anxiety has been much less investigated. However, the neuroanatomical distribution of NK3 receptors suggests a potential role of this receptor in the control of emotional processes. NK3 receptors are found in limbic structures, such as the amygdala and the hippocampus, areas traditionally implicated in the modulation of fear and anxiety. Moreover, NK3 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., 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 NK3 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 NK3 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 NK3 receptors may attenuate stress-related behaviors.

Several studies have investigated the behavioral effects of NK3 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 & De Lima, 1998) in some of these studies, whereas others have reported a lack of activity of NK3 receptor agonists (Ribeiro & De Lima, 2002; Ribeiro & De Lima, 1998). Even more intriguing is the finding that the peptide NK3 receptor antagonist [Trp7-β-Ala8]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 NK3 receptor is particularly remarkable for its pharmacological heterogeneity, an idea that is substantiated by the observation that the guinea pig and gerbil NK3 receptors exhibit a similar pharmacological profile to the human NK3 receptor, while that of the rat is somewhat different from the human NK3 receptor. Information on the NK3 receptor and its pharmacology in the mouse is lacking, thus precluding interspecies generalization of the behavioral effects of NK3 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 NK3 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 NK3 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 NK3 receptor ligands in depression. Moreover, the available data in laboratory animals are equivocal regarding the antidepressant potential of NK3 receptor ligands. One study has demonstrated that the NK3 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 NK3 receptor agonist is dependent upon the activity of the endogenous opioid system.

The finding of an antidepressant-like profile after NK3 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 (Dahleb et al., 2002). Moreover, osanetant was found active in the stress-induced tonic

Table 3
The effects of NK3 receptor-modulating drugs in anxiety models.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Species</th>
<th>Doses</th>
<th>Route, min</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurokinin B</td>
<td>Endogenous NK3 ligand</td>
<td>Elevated plus-maze</td>
<td>Mice</td>
<td>1–500 pmol/2 μl i.c.v., 5 o</td>
<td></td>
<td>(Ribeiro et al., 1999)</td>
</tr>
<tr>
<td>Senktide</td>
<td>NK3 agonist</td>
<td>Elevated plus-maze</td>
<td>Mice</td>
<td>10 pmol i.c.v., 5 +</td>
<td></td>
<td>(Ribeiro &amp; De Lima, 1998)</td>
</tr>
<tr>
<td>Senktide</td>
<td>Elevated plus-maze</td>
<td>Mice</td>
<td>100 pmol/2 μl i.c.v., 0 o</td>
<td></td>
<td></td>
<td>(Ribeiro &amp; De Lima, 2002)</td>
</tr>
<tr>
<td>Senktide</td>
<td>Elevated plus-maze</td>
<td>Mice</td>
<td>0.1–500 pmol/5 μl i.c.v., 5 +</td>
<td></td>
<td></td>
<td>(De Lima et al., 1995)</td>
</tr>
<tr>
<td>Senktide</td>
<td>Elevated plus-maze</td>
<td>Mice</td>
<td>100–500 pmol/2 μl i.c.v., 5 +</td>
<td></td>
<td></td>
<td>(Ribeiro &amp; De Lima, 2002)</td>
</tr>
<tr>
<td>[Trpβ-Ala8]NKA(4-10)</td>
<td>NK3 antagonist</td>
<td>Elevated plus-maze</td>
<td>Mice</td>
<td>100 pmol/2 μl i.c.v., 0 o</td>
<td></td>
<td>(Ribeiro &amp; De Lima, 2002)</td>
</tr>
<tr>
<td>[Trpβ-Ala8]NKA(4-10)</td>
<td>Elevated plus-maze</td>
<td>Mice</td>
<td>10 pmol/2 μl i.c.v., 5</td>
<td></td>
<td></td>
<td>(Ribeiro et al., 1999)</td>
</tr>
<tr>
<td>Osanetant</td>
<td>NK3 antagonist</td>
<td>Marble burying</td>
<td>Gerbils</td>
<td>1–10 mg/kg ip, 30 o</td>
<td></td>
<td>Unpublished</td>
</tr>
<tr>
<td>Osanetant</td>
<td>Stress-induced hyperthermia</td>
<td>Gerbils</td>
<td>1–10 mg/kg ip, 30 o</td>
<td></td>
<td></td>
<td>Unpublished</td>
</tr>
<tr>
<td>Osanetant</td>
<td>Social interaction</td>
<td>Gerbils</td>
<td>1–30 mg/kg ip, 30 o</td>
<td></td>
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<td>Unpublished</td>
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<tr>
<td>Osanetant</td>
<td>Elevated plus-maze</td>
<td>Mice</td>
<td>100 pmol/2 μl i.c.v., 5 +</td>
<td></td>
<td></td>
<td>(Salome et al., 2006)</td>
</tr>
<tr>
<td>Osanetant</td>
<td>Elevated plus-maze</td>
<td>Mice</td>
<td>1–500 pmol/2 μl i.c.v., 5 o</td>
<td></td>
<td></td>
<td>(Ribeiro &amp; De Lima, 1998)</td>
</tr>
<tr>
<td>Osanetant</td>
<td>Four-plate</td>
<td>Gerbils</td>
<td>20</td>
<td></td>
<td></td>
<td>Unpublished</td>
</tr>
<tr>
<td>SSR146977</td>
<td>NK3 antagonist</td>
<td>Social interaction</td>
<td>Gerbils</td>
<td>3–10 mg/kg po, 60 o</td>
<td></td>
<td>Unpublished</td>
</tr>
</tbody>
</table>

+ 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 NK3 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 NK3 receptor activation. Based on the above-mentioned observations that NK3 receptor stimulation triggers brain systems involved in the regulation of the stress response, antidepressant-like effects of NK3 receptor antagonists would be more in accordance with prediction. However, two phase II studies evaluating the potential of 50, 100 and/or 200 mg osanetan in severe depression proved non-conclusive. After six weeks of treatment, no significant difference was observed between osanetan (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 NK3 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 NK3 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-prefering rats (Ciccocioppo et al., 1994, 1995, 1997; Panocka et al., 1998; Perfumi et al., 1991). These latter effects were abolished by the peptide NK3 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 NK3 receptor agonists reduce ethanol intake by substituting the rewarding properties of ethanol (Massi et al., 2000). More recently, it was demonstrated that NK3 is associated with alcohol and cocaine dependence following the observation of polymorphisms in the NK3 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, osanetan was found to block the behavioral effects of cocaine in marmosets (De Souza Silva et al., 2006). The mechanisms underlying the action of NK3 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 NK3 receptor (Nwaneshiudu & Unterwald, 2006). To date, it is not known whether NK3 receptor antagonists may influence reward processes.

4. Conclusion

The NK3 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 NK3 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 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 NK3 system may be a factor. Perhaps, it is more reasonable to think that the selective blockade of the NK3 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 undesired 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 NK3 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 NK3 field by developing dual NK3/NK1 receptor antagonists, which could have improved efficacy when compared to selective NK3 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.

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