Neuropeptide Receptor Ligands for the Treatment of Schizophrenia: Focus on Neurotensin and Tachykinins

Guy Griebel*

Sanofi, Strategy, Science Policy & External Innovation, 1 Avenue Pierre Brossolette, 91385 Chilly-Mazarin, France

Abstract: There is a wealth of evidence that various neuropeptides and their receptor ligands modulate schizophrenia-related behaviors in preclinical animal models, suggesting that neuropeptide systems may represent potential novel therapeutic targets for the treatment of schizophrenia. In particular, neurotensin and tachykinins have been the subject of significant research efforts, generating compelling preclinical data in the schizophrenia field. However, clinical studies with notably selective tachykinin NK_3 receptor antagonists in schizophrenia 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 this condition. This article reviews preclinical and clinical findings on ligands for neurotensin and tachykinin receptors in schizophrenia, and provides possible explanations for the failure so far to develop small-molecule neuropeptide ligands for the treatment of schizophrenia.

Guy Griebel

Keywords: Neuropeptides, Neurotensin, NK3 receptor, Schizophrenia, Tachykinins.

INTRODUCTION

In the search for novel therapeutic approaches to the clinically used antipsychotics, it has been suggested that drugs that target certain neuropeptide systems could represent promising alternatives [1-3]. Neuropeptides regulate physiological processes throughout all phases of development. They act as neurohormones, neurotransmitters, and/or neuromodulators, maintain homeostasis and influence cognitive, emotional and behavioural functions, including hunger, thirst, sex drive, pleasure and pain [4]. Neuropeptides are synthesized and bind to specific targets within brain areas and are suggested to play a role in central nervous system (CNS) diseases. As they are sometimes colocalized in neurons synthesizing classical neurotransmitters that are related to some of these conditions, compounds interfering with neuropeptide functions have been developed as pharmacological tools intending to treat a variety of mental diseases, including schizophrenia. More than one hundred of them have been identified over the years, which can be classified according to their structure, function, or major sites of synthesis [4].

Similar to classical neurotransmitters, the majority of neuropeptides binds to seven-transmembrane G-protein-coupled receptors (GPCRs), although some action through ion channel-associated receptors has been reported. However, neuropeptides differ from classical neurotransmitters in several aspects and, as indicated above, it is important to mention that they can co-exist with classical neurotransmitters within the same neuron and can be co-transmitted [4, 5]. To better conceptualize the role of neuropeptides in schizophrenia and the therapeutic value of drugs acting at these neuropeptide systems for the treatment of this condition, it is important to discuss some of the differences between neuropeptide and classical neurotransmitter systems.

Unlike classical neurotransmitters, neuropeptides often act as local neuronal modulators as well as endocrine hormones, thus mediating complex integrated behaviours. Further, a paracrine mechanism of action of some specific neuropeptides with particular physiological actions has been described. This is for example the

case of neurotensin [6]. Other differences include biosynthesis, storage, axonal transport, release and inactivation. These differences are summarized in Table **1**. First, while classical neurotransmitters are synthesized from dietary precursors by specific enzymes in nerve terminals and, in some cases in perikarya, neuropeptides are synthesized in the cell body only from gene transcription and translation. Classical neurotransmitters are then stored in small vesicles, while neuropeptides are stored in large vesicles. The synthesizing enzymes as well as the storage vesicles of the classical neurotransmitters are then transported down the axon while, in the case of neuropeptides, only the storage vesicles are transported. The release dynamics also differ. Thus, when neurons fire at a slow rate, release is limited to small neurotransmitter vesicles. When burst firing and prolonged depolarization occurs, the calcium concentration in the presynaptic terminal is elevated, leading to the release of neuropeptide vesicles in addition to neurotransmitter. neuropeptides need conditions of relatively high neuronal discharge to be released at quantities, which activate their receptors, while classical neurotransmitters are already released by low neuronal firing [7]. This in turn implies that selective blockade of the receptor by neuropeptide antagonists should be without consequences under resting conditions (unless the antagonist has an intrinsic activity on its own), but should only have effects after activation of the targeted neuropeptidergic system, also at the behavioural level.

NEUROPEPTIDE SYSTEMS IN SCHIZOPHRENIA

There is a wealth of evidence that various neuropeptides and their receptor ligands modulate schizophrenia-related behaviors in preclinical animal models. Such neuropeptide systems include neurotensin, cholecystokinin, corticotropin releasing factor, neuropeptide Y, oxytocin, opioid peptides, tachykinins, thyrotropin-releasing hormone, and orexins. The specifics of these findings have been described in many comprehensive reviews [1-3]. Here we will focus on neurotensin and tachykinins, as studies on these systems have generated the most compelling preclinical data in the schizophrenia field. Moreover, selective nonpeptide antagonists for the type 3 receptor subtype of tachykinins (i.e. TACR3, also known as the NK_3 receptor), underwent clinical trials in schizophrenic patients. Here we present findings from an as yet unpublished Phase IIb clinical trial with the NK_3 receptor antagonist, osanetant.

*Address correspondence to this author at the Sanofi, Strategy, Science Policy & External Innovation, 1 Avenue Pierre Brossolette, 91385 Chilly-Mazarin, France; Tel: +33 6 73 68 97 96; Fax: +33 1 53 77 41 33; E-mail: guy.griebel@sanofi.com

Table 1. Comparison of the cellular processes (production, storage, transport, release and fate) between classical neurotransmitters and neuropeptides. Adapted from [4].

	Classical Neurotransmitters	Neuropeptides
Type of molecule	Small water-soluble molecules containing amine (amino acid transmitters) and carboxyl groups	Large molecules
Biosynthesis	Synthesized from dietary precursors by specific enzymes, mainly in nerve terminals, in some cases in perikarya	Transcripted and translated from prepropeptides genes. Then, after activation by peptidases, transformed in propeptide and finally, after activation of converting enzymes, neuropeptide is obtained. This process occurs in cell bodies or dendrites
Storage	In small vesicles	In large vesicles
Transport	Synthesizing enzymes as well as storage vesicles tranported down the axon	Packaged into vesicles and transported down the axon to the terminal
Release	Occurs through exocytosis at specialized regions (active zones) from the nerve terminal	Occurs through exocytosis, but no specific active zones
Possibility of paracrine action	No	Yes
Inactivation	Metabolism in synaptic cleft or reuptake by transporter and recycling	Broken down by membrane peptidases. No reuptake or re-use

Neurotensin in Schizophrenia

In 1973, the tridecapeptide neurotensin was first isolated from the bovine hypothalamus [8]. It was found to have a broad spectrum of physiological activities: acting as a neurotransmitter in the brain; behaving as a digestive hormone in the gut; and acting as a regulator of cardiac output and blood pressure in the cardiovascular system [9]. In the CNS, neurotensin is associated with several neurotransmitter systems, including dopaminergic, serotonergic, GABAergic, glutamatergic and cholinergicsystems [3, 10-12].

The effects of neurotensin are mediated by two G protein-coupled 7-TM domain receptors (neurotensin receptor 1 (NTR1) and NTR2) [13, 14], and a type I amino acid receptor (NTR3; also known as sortilin [15]). NTR1 has attracted much attention as it has a major role in the modulation of neurotransmitter systems [16]. Expressed in both neurons and glial cells, neurotensin is widely distributed throughout the CNS. High levels of expression are found in the substantia nigra, ventral tegmental area, lateral septum, bed nucleus of the stria terminalis as well as the prefrontal, cingulate, insular and suprarhinal cortices [17-20]. Much work has focused on the role of neurotensin in regulating dopaminergic function, an idea substantiated by findings that central administration of the peptide has behavioural effects mimicking those elicited by antipsychotics whose primary action is to regulate the mesocorticolimbic and neostriatal dopaminergic systems [10-12]. These observations have led to the idea that dysfunction of neurotensin neurotransmission in this system may be involved in the pathogenesis of schizophrenia, and suggest that neurotensin receptors, in particular the NTR1, may represent a novel target for the treatment of this condition.

Although most of the available NTR1 agonists are peptide analogues of neurotensin (NT_{8-13}) that have been modified to increase metabolic stability and CNS penetration, a few non-peptide NTR1 agonists have been designed [12, 21-24]. As with centrally administered neurotensin, these agonists have similar behavioural and neurochemical effects to antipsychotics in animal models of schizophrenia, with the added benefits of not causing catalepsy or weight gain— adverse events that are associated with some of the currently used antipsychotics [11, 25] (Table **2**). Instead, some of these compounds even decreased food intake. Surprisingly, there is some evidence that NTR1 antagonists may have antipsychotic-like ef-

fects, as suggested by the observation that prolonged NTR1 blockade produced an inhibition of firing rate in dopaminergic cells in the ventral tegmental area, similarly to haloperidol and clozapine, two pharmacologically different prototypical antipsychotics [26]. However, in a Phase IIa double-blind clinical trial the non-peptide NTR1 antagonist meclinertant (SR48692) was found to be inactive in the treatment of schizophrenia and schizoaffective disorder. It is noteworthy that, based on the hypothesis that neurotensin agonism has an antipsychotic effect, a worsening of psychosis might have been predicted in patients who received meclinertant compared with placebo, but this was not observed.

As of today no results from clinical trials with NTR1 agonists in schizophrenia have been disclosed. It is even doubtful that such drugs have been tested for their efficacy as antipsychotic in clinical trials. To the best of our knowledge, the neurotensin analogue NT69L is the only NTR1 agonist that has been evaluated in a Phase I trial [27]. The reports of this study were scarce but the drug produced some hypotension, which may have led to its discontinuation. Such an adverse effect may not be surprising as there has been some concern over the potential side effects of neurotensin receptor agonists due to the large number of peripheral neurotensin receptors known to be involved in the regulatation of blood pressure [11]. Another potential issue regarding the therapeutic efficacy of such drugs is the development of tolerance, which occurs rapidly (that is, after a single administration), as shown with NT69L in animal models of antipsychotic-like activity [11].

It is clear from the preclinical data that NTR1 agonists have the potential to represent an interesting option for the treatment of schizophrenia. However, the risk of producing side effects and the development of tolerance to the therapeutic effects, along with the difficulty in synthesizing non-peptide molecules with favourable properties, has led to termination of the clinical development programmes of NTR1 agonists by all players in the field.

Tachykinins in Schizophrenia

Preclinical Studies

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 CNS [28, 29]. These neuropeptides exert a plethora of biological effects,

Table 2.   Summary of effects of a peptide (NT69L) and a non-peptide (SSR107699) NT1R agonist in animal models of schizophrenia-related behaviors.

Drug	Binding IC_{50}, nM (Mouse)		Ago efficacy (IP) EC_{50}, nM	Behavioural effects (MED, mg/kg, i.p.)			
	NT1R	NT2R	NT1R	Amphetamine hyperactivity	PCP hyperactivity	PCP neonates	Food intake
NT69L	2	4	0.28	0.01	0.001	0.01	1
SSR107699	151	527	0.80	0.0025	0.0025	0.03	0.1

MED: minimal active dose; PCP neonates: this model investigates effects on attenuated selective attention deficit induced by neonatal PCP treatment; Food intake: the drugs decreased food intake. Unpublished data kindly provided by Drs Jean-Paul Terranova and Florence Oury-Donat (Sanofi R&D, Montpellier).

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. SP, NKA and NKB are widely distributed in the CNS, but they have distinct expression patterns. The highest concentrations of NKB are found in cortical areas, whereas substance P and NKA share a more similar distribution pattern, with strong expression in the spinal cord and in structures that are implicated in emotional processes (for example, the nucleus accumbens, septum and the amygdala). At a cellular level, substance P and NKA are mostly colocalized in neurons, including interneurons, with glutamate, GABA (γ-aminobutyric acid), monoamines or acetylcholine. The biological actions of substance P, NKA and NKB are mediated via the activation of G protein-coupled seven-transmembrane domain receptors designated as tachykinin receptor 1 (TACR1; also known as the NK_1 receptor), TACR2 (also known as the NK_2 receptor) and TACR3 (also known as the NK_3 receptor), respectively [30]. NK_1, NK_3 and, to a lesser extent, NK_2 receptors are widely distributed in the CNS. As will be described below, the NK_3 receptor has been the main focus for antipsychotic drug discovery on tachykinins. Here we will provide an overview on the therapeutic potential of NK_3 receptor antagonists in schizophrenia, by reviewing existing behavioral and neurochemical effects of these agents in both preclinical and clinical studies, and by presenting an as yet unpublished findings from a Phase IIb trial on the effects of the selective non-peptide NK_3 receptor antagonist osanetant in schizophrenic patients.

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 (for a review, see [31]). 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 [32, 33]. This species heterogeneity, has had a major impact on the development of specific antagonists for this receptor, as it required the development of suitable behavioural models in atypical species such as guinea pigs and gerbils to characterize their effects [31].

NK_3 receptors have a key role in dopaminergic functioning in the midbrain. They are found predominantly in the substantia nigra and the ventral tegmental area - regions of the brain that have a high concentration of dopaminergic neurons [31]. In fact, the distribution

of NK_3 receptor-like immunoreactivity in neurons in rats completely overlaps that of tyrosine hydroxylase immunoreactive neurons in the A8, A9 and A10 regions, suggesting a physiological modulation of dopaminergic neurons by tachykinins in these regions [35, 36]. This idea is substantiated by electrophysiological experiments in rats showing that the peptide NK_3 receptor agonist senktide produces excitatory effects when applied on a subpopulation of dopamine-sensitive neurons in the ventral tegmental area and in the substantia nigra [37-40]. Moreover, NK_3 receptor stimulation was shown to enhance spontaneous DA release in primary cultures of gerbil mesencephalon [41], increase the extracellular DA content in mesolimbic structures of guinea pigs [42] and elevate levels of DOPAC and the DOPAC/DA ratio in the striatum of rats when applied in the substantia nigra, indicating increased dopaminergic metabolism and turnover [43-45]. These results are strenghtened by behavioral studies demonstrating that senktide, when infused into the ventral tegmental area and the substantia nigra, produced behavioral effects similar to those obtained after dopaminergic activation, such as hyperactivity, rearing, sniffing, yawning and chewing [46-48]. Because excessive dopaminergic function is thought to play a major role in some of the symptoms of schizophrenia, it was hypothesized that NKB, the endogenous peptide for NK_3 receptors, may be involved in the pathophysiology of this condition [34]. Taken as a whole, these findings led logically to the idea that NK_3 receptor antagonists might have utility in the treatment of schizophrenia.

Osanetant was the first potent non-peptide NK_3 receptor antagonist described in the literature [49]. It was soon followed by the development of numerous various novel chemical classes of potent, competitive and selective non-peptide antagonists for the human NK_3 receptor [50-53]. In preclinical studies, osanetant has been shown to prevent overactivity of the dopaminergic system elicited by senktide infusion in regions containing DA cell bodies [38, 42]. Interestingly, the NK_3 receptor antagonist blocked the activation of DA cells in the A10 area caused by acute administration of the neurotensin receptor antagonist, SR142948 [54]. The behavioral effects of NK_3 receptor antagonists have been investigated in several animal models that are predictive of antipsychotic activity. For example, Man *et al.* [55] have used the prepulse inhibition (PPI) of the acoustic startle reflex in gerbils to demonstrate that osanetant is able to reverse 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 [56]. When osanetant was tested in this procedure using guinea pigs as subjects, it blocked conditioned avoidance response, suggesting antipsychotic-like effects [31].

CLINICAL STUDIES

Several NK_3 receptor antagonists have been evaluated in patients with schizophrenia [1]. Preliminary data in a special study

Table 3. Summary of primary and key secondary efficacy parameters following 8-week treatment of osanetant and risperidone in schizophrenic patients.

Parameter		Placebo (N=83)	Osanetant 50 mg (N=84)	Osanetant 200 mg (N=73)	Risperidone 4 mg (N=81)
	N patients at baseline and postbaseline	80	83	73	80
BPRS total score	Mean (SEM) at baseline	56.8 (0.82)	56.3 (0.85)	57.5 (1.06)	56.0 (0.82)
	LS-mean (SE)[a] at last visit	50.3 (1.25)	51.3 (1.23)	49.9 (1.31)	44.9 (1.25)
	LS-mean (SE)[a] change from baseline at last visit	-6.3 (1.25)	-5.3 (1.23)	-6.7 (1.31)	-11.7 (1.25)
	Difference from placebo (p-value)[a] [95% CI][a]		1.0 (0.568) [-2.4, 4.4]	-0.4 (0.810) [-4.0, 3.1]	-5.4 (0.002) [-8.9, -1.9]
CGI Severity of Illness score	Mean (SEM) at baseline	4.6 (0.08)	4.7 (0.07)	4.7 (0.08)	4.5 (0.06)
	LS-mean (SE)[a] at last visit	4.3 (0.11)	4.2 (0.11)	4.2 (0.11)	3.9 (0.11)
	LS-mean (SE)[a] change from baseline at last visit	-0.3 (0.11)	-0.4 (0.11)	-0.4 (0.11)	-0.8 (0.11)
	Difference from placebo (p-value)[a] [95% CI][a]		-0.1 (0.562) [-0.4, 0.2]	-0.1 (0.370) [-0.4, 0.2]	-0.5 (0.003) [-0.8, -0.2]
PANSS total score	Mean (SEM) at baseline	95.3 (1.41)	95.3 (1.48)	97.4 (1.85)	94.2 (1.44)
	LS-mean (SE)[a] at last visit	85.9 (2.05)	87.2 (2.02)	85.2 (2.16)	77.7 (2.06)
	LS-mean (SE)[a] change from baseline at last visit	9.5 (2.03)	-8.3 (2.00)	-10.6 (2.14)	-18.0 (2.05)
	Difference from placebo (p-value)[a] [95% CI][a]		1.2 (0.677) [-4.4, 6.8]	-1.1 (0.716) [-6.9, 4.7)	-8.5 (0.003) [-14.2, -2.81]
BPRS positive symptom cluster score	Mean (SEM) at baseline	16.0 (0.27)	16.0 (0.29)	15.8 (0.30)	15.7 (0.25)
	LS-mean (SE)[a] at last visit	13.7 (0.39)	13.7 (0.39)	13.4 (0.41)	11.7 (0.39)
	LS-mean (SE)[a] change from baseline at last visit	-2.2 (0.39)	-2.1 (0.39)	-2.4 (0.41)	-4.2 (0.39)
	Difference from placebo (p-value)[a] [95% CI][a]		(0.928) [-1.0, 1.1]	-0.3 (0.659) [-1.4, 0.9]	-2.0 (<.001) [-3.1, -0.9]

[a]LS-means (SE), difference from placebo, p-values and confidence intervals are based on the primary analysis usingan ANCOVA model which includes terms for baseline score and treatment.Each p-value and 95% CI are raw and unadjusted.To determine the significance of the comparisons of osanetant versus placebo, Bonferroni-Hommel procedure isused; that is, if both p-values of 50 mg and 200 mg groups are ≤0.05, then they are both declared significant at 0.05 level; or, if 1 p-value is >0.05, then the other p-value needs to be ≤2.5% to be significant at 0.05 level.ANOVA = analysis of variance; CI = confidence interval; CGI = Clinical Impression; BPRS = Brief Psychiatric RatingScale; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean; SE = stand error; LS = leastsquares.

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 [57]. Based on these findings, a second phase IIb clinical trial with osanetant was initiated.

The primary objective of the study was to evaluate the efficacy of two fixed doses of osanetant in patients with acute psychotic exacerbation of schizophrenia or schizoaffective disorder. The secondary objectives of the trial were to evaluate the efficacy of the drug on negative and affective symptoms, and its tolerability and

safety. The study was a multicenter, randomized, parallel-group, double-blind, Phase IIb trial that compared osanetant (50 mg per day and 200 mg per day) and risperidone (4 mg per day) with placebo for 8 weeks in a total of 321 patients. The primary efficacy parameter was the change from the baseline on Day 56, or last assessed visit in case of early termination, of the BPRS total score (extracted from the PANSS). As indicated in Table **3** an osanetant effect was not demonstrated (no significant difference between any osanetant dose and placebo). Risperidone consistently presented a steady reduction of BPRS total score. The evolution in change from baseline scores during treatment was similar for osanetant doses and placebo. Similarly, on the key secondary efficacy parameters (i.e. CGI Severity of Illness score, PANSS total score and BPRS positive symptom cluster score), analysis did not demonstrate a

significant effect of the NK_3 receptor antagonist (Table **3**). Risperidone was consistently superior in demonstrating reduction in these parameters during treatment. Importantly, however, osanetant was well tolerated. The most frequently occurring treatment-emergent adverse events in any treatment group were headache, dizziness, psychotic disorder, constipation, toothache, decreased appetite, and pain in extremity. There were no clinically relevant changes of laboratory parameters, vital signs, or ECGs. The results of this second, larger trial, which failed to demonstrate any significant efficacy of osanetant in schizophrenic patients, led to the discontinuation of the development of the drug.

Several Phase II trials have been performed with another NK_3 receptor antagonist, talnetant, in schizophrenia. An initial placebo-controlled study revealed that talnetant reduced the PANSS score to a similar extent as the antipsychotic drug risperidone, but this effect was not replicated in subsequent trials [58] so development was discontinued. More recently, AstraZeneca presented findings of another NK_3 receptor antagonist, AZD-2624, which was also inactive in a Phase IIa trial for schizophrenia [53].

CONCLUSION

Neuropeptide receptors, notably neurotensin NT1 and tachykinin NK_3 have been suggested many times to represent promising new targets for the treatment of schizophrenia. This idea was based in great part on data from preclinical studies highlighting that these receptors have diverse modulatory roles on a number of key neurotransmitter systems involved in the pathophysiology of this condition, in particular DA, findings which have led to these targets being progressed into the clinic. Unfortunately, taken as a whole, the available clinical findings, in particular with selective non-peptide NK_3 receptor antagonists in schizophrenia, have not convincingly established that the blockade of this neuropeptide receptor may be sufficient to improve these conditions. Among the most commonly noted reasons for the failure to successfully develop these neuropeptide receptor ligands for schizophrenia is their suboptimal pharmacokinetic characteristics, such as limited brain penetration, which may account at least in part for their poor efficacy in clinical trials. Perhaps, it is more reasonable to think that the selective blockade of a single neuropeptide receptor in the brain may not be sufficient to achieve significant therapeutic efficacy in schizophrenia. Considering that this approach has yielded few successes and that the current most effective antipsychotics (e.g., olanzapine, risperidone, aripiprazole) are relatively non-selective, the question arises whether the concept of designing maximally selective ligands to act on individual neuropeptide drug targets is the right paradigm in antipsychotic drug discovery.

Polypharmacology has emerged as a new paradigm in drug discovery to overcome the failure of the single target approach, in particular for complex multifactorial diseases, including schizophrenia [59, 60]. It is based on the idea that superior efficacy can be achieved by designing individual new chemical entities that can simultaneously address different targets of a given pathogenic cascade. The rational design of a desired multitarget drug remains today a complex and exceedingly difficult task for medicinal chemistry. However, new approaches for improving the design of ligands against profiles of multiples drug targets are emerging rapidly [61, 62]. We believe that this paradigm offers a new framework for thinking about how to innovate in antipsychotic drug discovery. Most pharmaceutical companies have halted their research efforts to find neuropeptide receptor ligands for schizophrenia, and there is currently no such molecule in clinical development for this condition. Today, only Roche seems to pursue some activities and is applying the polypharmacology paradigm to develop dual NK_1/NK_3receptor antagonists, which could have improved efficacy when compared to selective NK_3 receptor antagonists against schizophrenia [63].

REFERENCES

[1]   Griebel G, Holsboer F. Neuropeptide receptor ligands as drugs for psychiatric diseases: the end of the beginning? Nat Rev Drug Discov 2012; 11: 462-78.

[2]   Lacrosse AL, Olive MF. Neuropeptide systems and schizophrenia. CNS Neurol Disord Drug Targets 2013; 12(5): 619-32.

[3]   Caceda R, Kinkead B, Nemeroff CB. Involvement of neuropeptide systems in schizophrenia: human studies. Int Rev Neurobiol 2007; 78: 327-76.

[4]   Belzung C, Yalcin I, Griebel G, Surget A, Leman S. Neuropeptides in psychiatric diseases: an overview with a particular focus on depression and anxiety disorders. CNS Neurol Disord Drug Targets 2006; 5: 135-45.

[5]   Valentino RJ, Commons KG. Peptides that fine-tune the serotonin system. Neuropeptides 2005; 39: 1-8.

[6]   Heasley LE. Autocrine and paracrine signaling through neuropeptide receptors in human cancer. Oncogene 2001; 20: 1563-9.

[7]   Hokfelt T, Bartfai T, Bloom F. Neuropeptides: opportunities for drug discovery. Lancet Neurol 2003; 2: 463-72.

[8]   Carraway R, Leeman SE. The isolation of a new hypotensive peptide, neurotensin, from bovine hypothalami. J Biol Chem 1973; 248: 6854-61.

[9]   St Pierre S, Quirion R, Regoli D, *et al*. Neurotensin, a multi-action peptide hormone. Union Med Can 1980; 109: 1447-55.

[10]   Caceda R, Kinkead B, Nemeroff CB. Neurotensin: role in psychiatric and neurological diseases. Peptides 2006; 27: 2385-404.

[11]   Kinkead B, Nemeroff CB. Novel treatments of schizophrenia: targeting the neurotensin system. CNS Neurol Disord Drug Targets 2006; 5: 205-18.

[12]   Boules M, Shaw A, Fredrickson P, Richelson E. Neurotensin agonists: potential in the treatment of schizophrenia. CNS Drugs 2007; 21: 13-23.

[13]   Tanaka K, Masu M, Nakanishi S. Structure and functional expression of the cloned rat neurotensin receptor. Neuron 1990; 4: 847-54.

[14]   Chalon P, Vita N, Kaghad M, *et al*. Molecular cloning of a levocabastine-sensitive neurotensin binding site. FEBS Lett 1996; 386: 91-94.

[15]   Mazella J, Botto JM, Guillemare E, Coppola T, Sarret P, Vincent JP. Structure, functional expression, and cerebral localization of the levocabastine-sensitive neurotensin/neuromedin N receptor from mouse brain. J Neurosci 1996; 16: 5613-20.

[16]   Pettibone DJ, Hess JF, Hey PJ, *et al*. The effects of deleting the mouse neurotensin receptor NTR1 on central and peripheral responses to neurotensin. J Pharmacol Exp Ther 2002; 300: 305-13.

[17]   Boudin H, Pelaprat D, Rostene W, Beaudet A. Cellular distribution of neurotensin receptors in rat brain: immunohistochemical study using an antipeptide antibody against the cloned high affinity receptor. J Comp Neurol 1996; 373: 76-89.

[18]   Elde R, Schalling M, Ceccatelli S, Nakanishi S, Hokfelt T. Localization of neuropeptide receptor mRNA in rat brain: initial observations using probes for neurotensin and substance P receptors. Neurosci Lett 1990; 120: 134-8.

[19]   Fassio A, Evans G, Grisshammer R, Bolam JP, Mimmack M, Emson PC. Distribution of the neurotensin receptor NTS1 in the rat CNS studied using an amino-terminal directed antibody. Neuropharmacology 2000; 39: 1430-42.

[20]   Alexander MJ, Leeman SE. Widespread expression in adult rat forebrain of mRNA encoding high-affinity neurotensin receptor. J Comp Neurol 1998; 402: 475-500.

[21]   Tyler BM, Douglas CL, Fauq A, *et al*. *In vitro* binding and CNS effects of novel neurotensin agonists that cross the blood-brain barrier. Neuropharmacology 1999; 38: 1027-34.

[22]   Tyler-McMahon BM, Stewart JA, Farinas F, McCormick DJ, Richelson E. Highly potent neurotensin analog that causes hypothermia and antinociception. Eur J Pharmacol 2000; 390: 107-11.

[23] Machida R, Tokumura T, Tsuchiya Y, Sasaki A, Abe K. Pharmacokinetics of novel hexapeptides with neurotensin activity in rats. Biol Pharm Bull 1993; 16: 43-47.

[24] Tokumura T, Tanaka T, Sasaki A, Tsuchiya Y, Abe K, Machida R. Stability of a novel hexapeptide, (Me)Arg-Lys-Pro-Trp-tert-Leu-Leu-OEt, with neurotensin activity, in aqueous solution and in the solid state. Chem Pharm Bull (Tokyo) 1990; 38: 3094-8.

[25] Holly EN, Ebrecht B, Prus AJ. The neurotensin-1 receptor agonist PD149163 inhibits conditioned avoidance responding without producing catalepsy in rats. Eur Neuropsychopharmacol 2011; 21: 526-31.

[26] Michaud JC, Gueudet C, Soubrie P. Effects of neurotensin receptor antagonists on the firing rate of rat ventral pallidum neurons. Neuro Report 2000; 11: 1437-41.

[27] Richelson E. NT69L: A neurotensin receptor agonist for treatment of neuropsychiatric diseases. Neuropsychopharmacology 2005; 30: S50.

[28] Helke CJ, Krause JE, Mantyh PW, Couture R, Bannon MJ. Diversity in mammalian tachykinin peptidergic neurons: multiple peptides, receptors, and regulatory mechanisms. FASEB J 1990; 4: 1606-15.

[29] Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. Physiol Rev 1993; 73: 229-308.

[30] Regoli D, Boudon A, Fauchere JL. Receptors and antagonists for substance P and related peptides. Pharmacol Rev 199446: 551-99.

[31] Griebel G, Beeske S. Is there still a future for neurokinin 3 receptor antagonists as potential drugs for the treatment of psychiatric diseases? Pharmacol Ther 2012; 133: 116-23.

[32] Nguyen QT, Jukic D, Chretien L, Gobeil F, Boussougou M, Regoli D. Two NK-3 receptor subtypes: demonstration by biological and binding assays. Neuropeptides 1994; 27: 157-61.

[33] Suman-Chauhan N, Grimson P, Guard S, et al. Characterisation of [125I][MePhe7]neurokinin B binding to tachykinin NK3 receptors: evidence for interspecies variance. Eur J Pharmacol 1994; 269: 65-72.

[34] Spooren W, Riemer C, Meltzer H. Opinion: NK3 receptor antagonists: the next generation of antipsychotics? Nat Rev Drug Discov 2005; 4: 967-75.

[35] Chen LW, Guan ZL, Ding YQ. Mesencephalic dopaminergic neurons expressing neuromedin K receptor (NK3): a double immunocytochemical study in the rat. Brain Res 1998; 780: 150-4.

[36] Lessard A, Savard M, Gobeil F, Jr, Pierce JP, Pickel VM. 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 2009; 63: 484-501.

[37] Keegan KD, Woodruff GN, Pinnock RD. 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 1992; 105: 3-5.

[38] Nalivaiko E, Michaud JC, Soubrie P, Le Fur G, Feltz P. Tachykinin neurokinin-1 and neurokinin-3 receptor-mediated responses in guinea-pig substantia nigra: an in vitro electrophysiological study. Neuroscience 1997; 78: 745-57.

[39] Overton P, Elliott PJ, Hagan RM, Clark D. Neurokinin agonists differentially affect A9 and A10 dopamine cells in the rat. Eur J Pharmacol 1992; 213: 165-6.

[40] Seabrook GR, Bowery BJ, Hill RG. Pharmacology of tachykinin receptors on neurones in the ventral tegmental area of rat brain slices.Eur J Pharmacol 1995; 273: 113-9.

[41] Alonso R, Fournier M, Carayon P, Petitpretre G, Le Fur G, Soubrié P. Evidence for modulation of dopamine-neuronal function by tachykinin NK3 receptor stimulation in gerbil mesencephalic cell cultures. Eur J Neurosci 1996; 8: 801-8.

[42] Marco N, Thirion A, Mons G, et al. Activation of dopaminergic and cholinergic neurotransmission by tachykinin NK3 receptor stimulation: an in vivo microdialysis approach in guinea pig. Neuropeptides 1998; 32: 481-8.

[43] Bannon MJ, Brownschidle LA, Tian Y, et al. Neurokinin-3 receptors modulate dopamine cell function and alter the effects of 6-hydroxydopamine. Brain Res 1995; 695: 19-24.

[44] Humpel C, Saria A, Regoli D. Injection of tachykinins and selective neurokinin receptor ligands into the substantia nigra reticulata increases striatal dopamine and 5-hydroxytryptamine metabolism. Eur J Pharmacol 1991; 195: 107-14.

[45] Humpel C, Saria A. 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 1993; 157: 223-6.

[46] Elliott PJ, Mason GS, Stephens-Smith M, Hagan RM. Behavioural and biochemical responses following activation of midbrain dopamine pathways by receptor selective neurokinin agonists. Neuropeptides 1991; 19: 119-26.

[47] Liminga U, Johansson PE, Gunne L. Intranigral tachykinin NK3 receptor agonist elicits oral movements in rats. Pharmacol Biochem Behav 1991; 38: 617-20.

[48] Stoessl AJ, Szczutkowski E, Glenn B, Watson I. Behavioural effects of selective tachykinin agonists in midbrain dopamine regions. Brain Res 1991; 565: 254-62.

[49] Emonds-Alt X, Bichon D, Ducoux JP, et al. SR 142801, the first potent non-peptide antagonist of the tachykinin NK3 receptor. Life Sci 1995; 56: L27-32.

[50] Dawson LA, Smith PW. Therapeutic utility of NK3 receptor antagonists for the treatment of schizophrenia. Curr Pharm Des 2010; 16: 344-57.

[51] Juhl K, Hansen T, Kehler J, et al. Identification of a new series of non-peptidic NK3 receptor antagonists. Bioorg Med Chem Lett 2011; 21: 1498-501.

[52] Malherbe P, Ballard TM, Ratni H. Tachykinin neurokinin 3 receptor antagonists: a patent review (2005 - 2010). Expert Opin Ther Pat 2011; 21: 637-55.

[53] Simonsen KB, Juhl K, Steiniger-Brach B, Nielsen SM. Novel NK3 receptor antagonists for the treatment of schizophrenia and other CNS indications. Curr Opin Drug Discov Develop 2010; 13: 379-88.

[54] Gueudet C, Santucci V, Soubrie P, Le Fur G. Blockade of neurokinin3 receptors antagonizes drug-induced population response and depolarization block of midbrain dopamine neurons in guinea pigs. Synapse 1999; 33: 71-79.

[55] Man J, Jurzak M, Stohr T. The NK3 receptor antagonist SR142801 reverses apomorphine-induced deficits on prepulse inhibition in gerbils. Behav Pharmacol 2000; 11: 343.

[56] Van der Heyden JA, Bradford LD. 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 1988; 31: 61-67.

[57] Meltzer HY, Arvanitis L, Bauer D, Rein W. Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. Am J Psychiatry 2004; 161: 975-84.

[58] Evangelista S. Talnetant GlaxoSmithKline. Curr Opin Investig Drugs 2005; 6: 717-21.

[59] Youdim MB, Buccafusco JJ. Multi-functional drugs for various CNS targets in the treatment of neurodegenerative disorders. Trends Pharmacol Sci 2005; 26: 27-35.

[60] Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol 2008; 4: 682-90.

[61] Bottegoni G, Favia AD, Recanatini M, Cavalli A. The role of fragment-based and computational methods in polypharmacology. Drug Discov Today 2012; 17: 23-34.

[62] Besnard J, Ruda GF, Setola V, et al. Automated design of ligands to polypharmacological profiles. Nature 2012; 492: 215-20.

[63] Malherbe P, Knoflach F, Hernandez MC, et al. Characterization of RO4583298 as a novel potent, dual antagonist with in vivo activity at tachykinin NK1 and NK3 receptors. Br J Pharmacol 2011; 162: 929-46.