ELSEVIER

European Journal of Pharmacology 375 (1999) 51–60

ejp

www.elsevier.nl/locate/ejphar

Review

The tachykinin NK_1 receptor in the brain: pharmacology and putative functions

Alois Saria *

Division of Neurochemistry at the Department of Psychiatry, University Hospital Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria

Accepted 30 April 1999

Abstract

After its discovery in 1931, substance P (SP) remained the only mammalian member of the family of tachykinin peptides for several decades. Tachykinins thus refer to peptides sharing the common C-terminal amino acid sequence Phe–X–Gly–Leu–Met · NH_2. In recent years the family of mammalian tachykinins has grown with the isolation of two novel peptides from bovine and porcine central nervous system (CNS), neurokinin A and neurokinin B. In parallel with the identification of multiple endogenous tachykinins several classes of tachykinin receptors were discovered. The receptors described so far are named tachykinin NK_1 receptor, tachykinin NK_2 receptor and tachykinin NK_3 receptor, respectively. The present review focuses on the pharmacology and putative function of tachykinin NK_1 receptors in brain. The natural ligand with the highest affinity for the tachykinin NK_1 receptor is SP itself. The C-terminal sequence is essential for activity, the minimum length of a fragment with reasonable affinity for the tachykinin NK_1 receptor is the C-terminal hexapeptide. A rapid advance of knowledge was caused by development of non-peptidic tachykinin NK_1 receptor antagonists. This area is under rapid development and a variety of different chemical classes of compounds are involved. Species-dependent affinities of tachykinin NK_1 receptor antagonists reveal two clusters of compounds, targeting the tachykinin NK_1 receptor subtype found in guinea pig, human or ferret or the one in rat or mouse, respectively. The most recently developed compounds are highly selective, enter the brain and are orally bioavailable. Distinct behavioural effects in experimental animals suggest the involvement of tachykinin NK_1 receptors in nociceptive transmission, basal ganglia function or anxiety and depression. Recent clinical trials in man showed that tachykinin NK_1 receptor antagonists are effective in treating depression and chemotherapy-induced emesis. Therefore, it is well possible that tachykinin NK_1 receptor antagonists will be clinically used for treatment of specific CNS disorders within a short period of time. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Tachykinin NK_1 receptor; Tachykinin; Neurokinin; Brain; Basal ganglia; Anxiety; Depression; Emesis; Non-peptidic antagonist

1. Introduction

After its discovery in 1931, substance P (SP) remained the only mammalian member of the family of tachykinin peptides for several decades. Tachykinins thus refer to peptides sharing the common C-terminal amino acid sequence Phe–X–Gly–Leu–Met · NH_2 (Table 1). In recent years the family of mammalian tachykinins has grown with the isolation of two novel peptides from bovine and porcine central nervous system (CNS), neurokinin A and neurokinin B (McLean, 1996). In parallel with the identification of multiple endogenous tachykinins several classes of tachykinin receptors were discovered. It has been observed that SP and the non-mammalian tachykinins eledoisin and kassinin exhibited different agonist potencies depending on the used bioassay system (McLean, 1996). Iversen et al. (see Lee et al., 1986; McLean, 1996), identified two distinct tachykinin potency profiles in smooth muscle preparations and proposed the existence of SP-P and SP-E receptors. Evidence for the existence of the two pharmacologically distinguishable sites was further provided by binding experiments with peptide radioligands (Beaujouan et al., 1986; Danks et al., 1986). With the discovery of a third binding site (Laufer et al., 1986) and the isolation of novel mammalian tachykinins, some by several groups in parallel, the nomenclature of tachykinins and their receptors became completely confusing. In 1984, at the tachykinin symposium in Montreal the following nomenclature was proposed (McLean, 1996). The endogenous mammalian tachykinins were designated as neu-

* Tel.: +43-512-504-3710; Fax: +43-512-504-3716; E-mail: alois.saria@uibk.ac.at

0014-2999/99/$ - see front matter © 1999 Elsevier Science B.V. All rights reserved.
PII: S0014-2999(99)00259-9

Table 1
Mammalian and non-mammalian tachykinins

Tachykinin	Sequence
Substance P	Arg–Pro–Lys–Pro–Gln–Gln–**Phe**–Phe–Gly–**Leu**–**Met**–$\mathbf{NH_2}$
Neurokinin A	His–Lys–Thr–Asp–Ser–**Phe**–Val–**Gly**–**Leu**–**Met**–$\mathbf{NH_2}$
Neurokinin B	Asp–Met–His–Asp–Phe–**Phe** Val–**Gly**–**Leu**–**Met**–$\mathbf{NH_2}$
Eledoisin	pGlu–Pro–Ser–Lys–Asp–Ala–**Phe**–Ile–**Gly**–**Leu**–**Met**–$\mathbf{NH_2}$
Kassinin	Asp–Val–Pro–Lys–Ser–Asp–Gln–**Phe**–Val–**Gly**–**Leu**–**Met**–$\mathbf{NH_2}$

rokinin A (previously also referred to as neurokinin α, neuromedin L or substance K) and neurokinin B (previously also named neurokinin β or neuromedin K). Furthermore, the receptors would be referred to as tachykinin NK_1 receptor (previously SP-P), tachykinin NK_2 receptor (previously SP-E, SP-K, NK-A) and NK_3 (previously also SP-E, SP-N, NK-B). SP is the most potent tachykinin for the tachykinin NK_1 receptor, whereas neurokinin A exhibits the highest affinity for the tachykinin NK_2 receptor and neurokinin B for the tachykinin NK_3 receptor, respectively. It has, however, to be pointed out clearly that all mammalian tachykinins have limited selectivity for a particular neurokinin receptor. Table 2 summarizes this limited selectivity. It is important to note that despite the early evidence for a cross-talk between different tachykinins at the different receptors, the tachykinin NK_1 receptor was de facto considered to be the SP receptor and, in other words, SP to be the physiological ligand for the tachykinin NK_1 receptor. In accordance, similar conclusions were applied to neurokinin A and the tachykinin NK_2 receptor, and neurokinin B and the tachykinin NK_3 receptor (Maggi and Schwartz, 1997). This dogma was so well established that homologous binding experiments using the 'wrong' tachykinin were not performed on the cloned receptors until recently (Maggi and Schwartz, 1997). With this in mind, it seems extremely difficult to sort out a particular function for one of the tachykinin peptides. Thus, it seems more rational to focus on the distribution and pharmacology of particular tachykinin receptors. Due to the more abundant distribution of tachykinin NK_1 receptors (Quartara and Maggi, 1998) and the variety of available synthetic agonists and antagonists for this tachykinin receptor (McLean, 1996; Maggi and Schwartz, 1997; Quartara and Maggi, 1997, 1998), this review predominantly describes tachykinin NK_1 receptor pharmacology. The distribution and putative function of tachykinin NK_1 receptors in the peripheral nervous system and in the gut has been recently discussed extensively in several reviews (McLean, 1996; Quartara and Maggi, 1997, 1998). The present review therefore focuses on the pharmacology and putative function of tachykinin NK_1 receptors in the CNS.

Table 2
Ligand–receptor interactions among mammalian tachykinins and receptors (from Maggi and Schwartz, 1997)

	NK_1	NK_2	NK_{3A}	NK_{3B}
SP	0.05–0.5	n.a.	n.a.	n.a.
NKA	0.5	0.8	n.a.	n.a.
NKB	0.5	n.a.	1.1	0.8

The indicated affinities for substance P (SP) and neurokinin (NK) A are based on homologous radioligand-binding experiments. For the tachykinin NK_3 receptors, indicated affinities are based on EC_{50} values for the stimulation of phosphatidyl inositol turnover in transfected cells (data concerning binding of neurokinin B in homologous radioligand-binding experiments are not available). The first tachykinin NK_3 receptor to be recognized is termed NK_{3A} (Maggi and Schwartz, 1997), the highly homologous, recently identified, tachykinin receptor NK_{3B} (Krause et al., 1997).

2. Distribution of tachykinin NK_1 receptors in the CNS

The distribution of tachykinin NK_1 receptors in the mammalian CNS has been investigated by autoradiography (Dam and Quirion, 1986; Danks et al., 1986; Saffroy et al., 1988), by studying the expression of messenger ribonucleic acid (mRNA) encoding for the receptor (Sivam and Krause, 1992; Aubry et al., 1994; Whitty et al., 1995; Whitty et al., 1997) and by immunohistochemistry (Shigemoto et al., 1993). Basically, the different approaches revealed comparable results and have provided evidence for a wide, but distinct distribution of receptors in various brain areas. Particularly rich in tachykinin NK_1 receptors are the striatum, the nucleus accumbens, the hippocampus, the lateral nucleus of the hypothalamus, the habenula, the interpeduncular nucleus, the nucleus of the tractus solitarius, the raphe nuclei and the medulla oblongata (Otsuka and Yoshioka, 1993). The expression of the mRNA encoding for the tachykinin NK1 receptor undergoes marked postnatal changes in the immature rat brain, supporting a possible role in the synaptic plasticity associated with morphological and functional CNS development (Herkenham, 1987). An interesting aspect is an apparent mismatch between the distribution of SP and tachykinin NK_1 receptors in the CNS (Herkenham, 1987). Such mismatches involve either the presence of SP immunoreactive nerve endings in areas which are tachykinin NK_1 receptor-negative (e.g., substantia nigra) or the presence of such receptors in CNS regions that are apparently not innervated by SP-containing nerves (hilus of dendate gyrus). Reasons for this mismatch could be technical factors, as in fact some tachykinin NK_1 receptors were very recently described by refined methods in substantia nigra

(Bannon and Whitty, 1995; Futami et al., 1998). In addition, the extensive cross-talk discussed above might be another reason for an apparent mismatch that could be no mismatch at all.

3. Properties of the tachykinin NK_1 receptor

The pharmacological criteria to define a tachykinin NK_1 receptor originate from the analyses of the rank order of potencies of natural mammalian and non-mammalian tachykinins and their fragments on binding and various bioassays, preferably in vitro, but in some instances also in vivo (Maggi et al., 1987; Regoli et al., 1987, 1988, 1989; Regoli and Nantel, 1991; Quartara and Maggi, 1997). The tachykinin NK_1 receptor has been cloned from several species including man (Yokota et al., 1989; Hershey and Krause, 1990; Maggi et al., 1993; Regoli et al., 1994). Species-related variations exist in the primary sequence of the tachykinin NK_1 receptor. Interestingly, these variations do not affect the potency or efficacy of agonists, but severely influence the potency of non-peptide antagonists in different species (see below).

4. Ligands for the tachykinin NK_1 receptor

The natural ligand with the highest affinity for the tachykinin NK_1 receptor is SP itself. The C-terminal sequence is essential for activity, the minimum length of a fragment with reasonable affinity for the tachykinin NK_1 receptor is the C-terminal hexapeptide (see Table 1). As discussed above, neurokinin A and neurokinin B do possess considerable affinity for the tachykinin NK_1 receptor as well. Therefore, synthesis of more selective ligands targeting one of the tachykinin receptor subtypes was successfully attempted (Quartara and Maggi, 1997). Such more selective agonists served to further characterize tachykinin receptor subtypes pharmacologically. In the early 1980s, modification of the peptide sequences of tachykinins were performed to produce tachykinin antagonists. Among several, one of the early useful compounds was Spantide (Maggi et al., 1991). The use of these compounds provided evidence for the involvement of endogenous neurokinin-receptor ligands in peripheral inflammation in the skin and airways (Lundberg et al., 1983; Lundberg et al., 1984; Saria, 1984; Lundberg and Saria, 1987). More potent peptidergic compounds possessing tachykinin NK_1 receptor antagonistic activity have been reported more recently (Lavielle et al., 1994). Many of the peptidic antagonists suffered, however, from poor potency, poor selectivity among neurokinin receptors, neurotoxicity at higher concentrations, and other problems associated with peptides, i.e., poor penetration into specific compartments, especially the CNS, and metabolic stability.

5. Non-peptide tachykinin NK_1 receptor antagonists

The story of non-peptide antagonists for the tachykinin receptors started in 1991, when several different groups almost at the same time reported compounds possessing tachykinin receptor-antagonistic properties (Maggi et al., 1993; Regoli et al., 1994). As this area is under rapid development and a variety of different chemical classes of compounds are involved, such substances may be classified by basic structures. Basically, the first of the antagonists were found by screening of chemical collections of compounds, e.g., at pharmaceutical companies such as Pfizer (CP 96345) (Snider et al., 1991) or Rhône-Poulenc (RP67580) (Garret et al., 1991). Among the chemical classes involved are steroids, perhydroisoindolones, benzylamino and benzylether quinuclidines, benzylamino piperidines, benzylether piperidines, other piperidine-based structures and tryptophan-based structures (Quartara and Maggi, 1997). The review by Quartara and Maggi (1997) lists 38 non-peptidic compounds with tachykinin-antagonistic properties with a detailed description. Additional new compounds with even improved pharmacological properties have recently been published (Iyengar et al., 1997; Hosoki et al., 1998; Kramer et al., 1998; Walpole et al., 1998a,b). Therefore, this review emphasizes the key features only and those compounds that have been used to obtain important data relevant to the reviewed issues of the CNS.

6. Species-dependent affinities of tachykinin NK_1 antagonists reveal two clusters of compounds

The cloned human and rat tachykinin NK_1 receptors show about 95% homology, i.e. 21 out of 407 amino acid residues differ between these two species. The majority of these residues is localized at the C- and N-terminal ends of the receptor protein. When analyzing the transmembrane segments 1–7, only six amino acids differ between these two species. With one exception (266 in transmembrane segment 6, i.e., valine in rat and isoleucine in mouse) the mouse and rat tachykinin NK_1 receptor have the identical amino acid sequence in transmembrane segments (Sundelin et al., 1992). In contrast, the guinea pig tachykinin NK_1 receptor is 97% homologous to the human tachykinin NK_1 receptor and 100% identical in transmembrane segments 1–7 (Gorbulev et al., 1992). In fact, clustering of various species (guinea pig and man vs. rat and mouse) related to heterogeneity in amino acid sequence of transmembrane segments 1–7 exactly matches the clustering of species-related differences in the affinities of non-peptidic tachykinin NK_1 receptor antagonists (Table 3). Finally, it has been shown that the species-related affinities of *cis*-3-(2-methoxybenzyl-amino-2-benzhydrylquinuclidine (CP 96345) (rat/mouse type) and 7,7-diphenyl-2 [1-imino-2

Table 3
Species selectivity in binding to tachykinin NK_1 receptors

Compound	K_I (nM)		
	Human tachykinin NK_1 receptor	Rat tachykinin NK_1 receptor	Ca^{2+} channels
CP 96,345	0.25	27	27
CP 99,994	0.25	136	3010
(±) RP 67,580	83	4	200
SR 140333	0.9	0.027	–
WIN 51708	> 25,000	21	–
L 709,210	0.7	–	190
L 760,735[a]	0.3–0.5	–	–
MK869[a]	0.3–0.5	–	–
SDZ NKT 343[b]	0.62	451	–

Antagonists also differ in their affinity of the rat Ca^{2+} channel. Data from McLean (1996), [a]Kramer et al. (1998) and [b]Walpole et al. (1998b).
SR 140333 = (*S*)1-(2-[3-(3,4-dichlorophenyl)-1-(3-isopropoxyphenylacetyl)piperidine-3-yl]ethyl)-4-phenyl-1-azoniabicyclo[2.2.2]octane chloride. Chemical names of other compounds are given in the text.

(2-methoxy-phenyl)-ethyl] perhydroisoindol-4-one (3*aR*, 7*aR*) (RP 67580) (human/guinea pig type) are linked to discrete positions of the tachykinin NK_1 receptor protein. These positions are amino acid positions 116 and 290 which contain (Val) and (Ile) in the human receptor and (Leu) and (Ser), respectively, in the rat/mouse receptor (Fong et al., 1992; Sachais et al., 1993). In addition, replacing the respective amino acids of the human receptor by the corresponding ones of the rat receptor, and vice versa, switched the affinities of CP 96345 and RP 67580 as expected (Fong et al., 1992; Sachais et al., 1993). In these mutant receptors, the affinity of SP remained unchanged, indicating that the variant amino acid residues are not crucial for the agonist binding. This also explains why these species-related subtypes had not been discovered earlier in a variety of bioassays in rat or guinea pig using all kinds of tachykinin NK_1 receptor agonists. Studies with other antagonists such as N^2-[(4*R*)-4-hydroxy-1-(1-methyl-1 *H*-indol-3-yl)carbonyl-L-prolyl]-*N*-phenylmethyl-3-(2-naphthyl)-L-alaninamide (FK 888), 17-beta-hydroxy-17 α-ethynyl-5 α-androstanol [3,2*b*] pyrimido[1,2*a*] benzimidazole (WIN 51708) confirmed this conclusion, further demonstrating that the described amino acid residues determine the species selectivity of compounds with entirely different chemical nature (Sachais and Krause, 1994; Jensen et al., 1994; Pradier et al., 1995).

7. Signal transduction coupling of the tachykinin NK_1 receptor

It is well established that the binding of tachykinin receptor agonists is regulated by guanine nucleotides indicating coupling to G-proteins (Guard and Watson, 1991). More recent findings from desoxyribonucleic acid cloning and functional expression experiments of all three tachykinin receptors provide clear evidence for this view (Macdonald and Boyd, 1989; Kwatra et al., 1993; Mochizuki et al., 1994; Macdonald et al., 1996). The stimulation of tachykinin NK_1 receptors activates several second messenger systems that are stimulation of phosphatidyl inositol turnover via phospholipase C, arachidonic acid mobilization via phospholipase A_2 and cyclic adenosine monophosphate accumulation via adenylyl cyclase (Nakajima et al., 1992; Mitsuhashi et al., 1992; Takeda et al., 1992; Seabrook and Fong, 1993; Garcia et al., 1994; Mochizuki et al., 1994).

8. Tachykinin NK_1 receptors in the spinal cord and their involvement in nociception

Originally, the newly developed non-peptidic tachykinin NK_1 receptor antagonists were tested for putative antinociceptive effects as SP has repeatedly been proposed as a 'pain transmitter'. However, the situation turned out to be extremely complicated and the efficacy of different tachykinin NK_1 receptor antagonists as antinociceptive compounds has been found to be poor in some instances. This review does not go into details of this complex issue, but refers to some recent reviews that extensively cover the problem of neurokinins and tachykinin NK_1 receptor antagonists in nociception (Longmore et al., 1997; Maggi, 1997; Quartara and Maggi, 1998).

As summarized by Quartara and Maggi (1998), evidence for the involvement of tachykinin NK_1 receptors in nociceptive transmission can be listed as follows: (1) tachykinin NK_1 receptors are expressed at appropriate anatomical locations to be considered for involvement in the processing of afferent noxious input in the spinal cord. Second order sensory neurons receiving a nociceptive input preferentially express tachykinin NK_1 receptors as compared to neurons receiving a non-noxious input. (2) Spinal cord tachykinin NK_1 receptor expression undergoes regulation after noxious manipulation. (3) The signal transmitted by activation of tachykinin NK_1 receptors is a slowly developing sustained depolarization, while the fast synaptic input to second order sensory neurons is mediated

by excitatory amino acids. (4) Functional or biochemical responses of second order sensory neurons to tachykinin NK_1 receptor activation are enhanced by peripheral tissue injury or inflammation. (5) Tachykinin NK_1 receptor antagonists act synergistically to inhibition of *N*-methyl-D-aspartate (NMDA)-mediated nociceptive transmission. (6) Tachykinin NK_1 receptor antagonists exhibit weak potency (Radhakrishnan et al., 1998) in acute pain, whereas antinociception can only be observed in nociceptive behavioural paradigms after induction of a persistent peripheral inflammation, i.e., models of 'chronic pain'. (7) This view has been confirmed recently with the new and even more selective compound 2-nitrophenylcarbamoyl-(*S*)-prolyl-(*S*)-3-(2-naphthyl)alanyl-*N*-benzyl-*N*-methylamide (SDZ NKT 343) (Walpole et al., 1998a). Several neurokinins are simultaneously released from spinal cord after nociceptive stimulation (Hua et al., 1986; Saria et al., 1986) and this release is modified by tachykinin NK_1 receptor antagonists (Malcangio and Bowery, 1994). Although data are still preliminary, some effects of tachykinin NK_1 receptor antagonists in dural inflammation suggest a putative role of tachykinin NK_1 receptors in migraine (McLean, 1996; Phebus et al., 1997). However, this view could not be confirmed in a clinical study using one particular tachykinin NK_1 receptor antagonist (Lanepitant) (Goldstein et al., 1997).

9. Tachykinin NK_1 receptor agonists and behaviour

The abundant distribution of tachykinin NK_1 receptors in brain is reflected by a wide variety of behavioural changes after central administration of SP or selective tachykinin NK_1 receptor agonists. Locomotion, grooming, wet-dog shakes, hind paw tapping, in some instances species related, have been observed after central administration of tachykinin NK_1 receptor agonists, probably related to the release of other transmitters such as dopamine, serotonin, or acetylcholine (Elliott and Iversen, 1986; Elliott et al., 1992; Bristow and Young, 1994; Stoessl et al., 1995; Piot et al., 1995). Although these behavioural studies with agonists indicate some distinct pharmacological effects of tachykinin NK_1 receptor activation, physiological or pathophysiological roles are difficult to conclude from these data.

10. Conclusions from tachykinin NK_1 receptor knockout mice

Investigation of behaviour of mice after targeted disruption of the gene for the tachykinin NK_1 receptor revealed further insight into putative functions (De et al., 1998). Interestingly, in these mice the behavioural responses to acute nociceptive thermal, mechanical or chemical stimuli (hot plate, tail flick, tail pinch, and writhing test) appear to be normal. A minor effect (30% decrease of the behavioural response to the second phase of the formalin paw test) could be detected. This is in line with the pharmacological data discussed above that the tachykinin NK_1 receptor has probably little importance in acute pain. Furthermore, the tachykinin NK_1 receptor knockout mice exhibited a lack of amplification mechanisms of noxious stimuli, as determined by electrophysiology. Additionally, a reduction of central inhibition (increased excitability of withdrawal reflexes) and a hyperalgesia in the contralateral paw after induction of inflammation and a reduction of stress-induced analgesia have been observed.

11. Behavioural and other central effects of tachykinin NK_1 receptor antagonists

An even more detailed picture of the putative physiological and pathophysiological roles of the tachykinin NK_1 receptor in brain can be obtained from the experiments with tachykinin NK_1 receptor antagonists. There have been several drawbacks of earlier compounds due to unspecific side effects, poor solubility and poor penetration into the CNS after systemic administration. However, the compounds developed more recently seem to be not only highly specific, but also penetrating the CNS and, as for the most recent human/guinea pig tachykinin NK_1 receptor preferring bis(trifluoromethyl) morpholine compound (MK-869), also long lasting and orally bioavailable (Kramer et al., 1998). Jacoby et al. (1997) have even proposed a way of designing water-soluble structures with tachykinin NK_1 receptor antagonistic properties. Generally, more firm data relating the putative functions of tachykinins in brain originate from pharmacological (i.e., behavioural) effects of the recent generation of potent and selective tachykinin NK_1 receptor antagonists. Trying to summarize the data available from experiments with different compounds, different routes of administration and different behavioural tests, it seems that blockade of tachykinin NK_1 receptors does not cause dramatic changes in gross behaviour of experimental animals (Quartara and Maggi, 1998). However, distinct changes in more refined behavioural paradigms have been reported and will be reviewed further below.

12. Basal ganglia-related effects and mechanisms

The basal ganglia represent a brain area where high concentrations of both tachykinins and neurokinin receptors can be detected. As a result, many studies have been performed in this area and attempts were made to relate mechanisms involving tachykinins and tachykinin receptors to extrapyramidal motor diseases such as Parkinson's disease and Chorea Huntington. Interactions between the meso-striatal dopamine system and tachykinins have been

observed with a number of interdisciplinary approaches. Lesions of striato-nigral γ-aminobutyric acid neurons containing SP lead to an upregulation of tachykinin NK_1 receptor mRNA in the substantia nigra (Whitty et al., 1995). Chronic treatment of rats with antipsychotic agents with extrapyramidal side effects leads to an upregulation of the genes encoding for tachykinins as well as for tachykinin NK_1 receptors (Bannon et al., 1986, 1987; Haverstick et al., 1989; Sivam et al., 1989; Humpel et al., 1990; Marksteiner et al., 1992, 1993). Clozapine, an antipsychotic agent lacking extrapyramidal side effects, in contrast, did not modify basal ganglia tachykinin expression (Humpel et al., 1990), indicating that the alterations in gene expression of tachykinins reflect the extrapyramidal motor effects of neuroleptic drugs. In agreement with this view, it has been reported that stimulation of oral movements after intranigral injection of a tachykinin NK_1 receptor agonist is enhanced in rats after chronic treatment with neuroleptics (Liminga and Gunne, 1993). This increase in agonist sensitivity may suggest that tachykinin NK_1 receptor antagonists may be useful in treating dyskinesia accompanied with treatment of humans with neuroleptic drugs. In fact, in animal experiments, the catalepsy induced by administration of a dopamine D_2 antagonist in rats could be inhibited by the tachykinin NK_1 receptor antagonist CP 99994, presumably by inhibiting striatal acetylcholine release (Anderson et al., 1995). Indirect support for this hypothesis comes from a study investigating SP on activity of midbrain dopamine neurons that has been found to act opposite of antipsychotic agents (Minabe et al., 1996). Although a direct involvement of tachykinins in the pathophysiology of Parkinson's disease was suggested for about 10 years, and a large amount of data was collected to provide circumstantial evidence (Barker, 1986, 1990, 1991, 1996), no firm conclusions can be made from these data and the evidence for such a contribution still remains poor.

13. Anxiety and depression

Recent studies with non-peptidic tachykinin NK_1 receptor antagonists suggested a putative anxiolytic effect (Teixeira et al., 1996; File, 1997) although this could not be demonstrated earlier possibly due to the sedative and motor impairing effect of one of the early compounds (Zernig et al., 1992, 1993; Saria et al., 1993). The recent data are compatible with the anxiogenic profile of centrally administered SP on the elevated plus maze (Elliott and Iversen, 1986). A significant step forward concerning the involvement of tachykinins in anxiety and depression is represented by the recent publication of Kramer et al. (1998). In this paper, evidence has been provided that a new, specific, long-lasting and orally bioavailable tachykinin NK_1 receptor antagonist, MK-869 reduces vocalization in guinea pig pups after maternal separation. It is established that this behavioural response is sensitive to psychotropic drugs that alleviate not only symptoms of anxiety and depression in humans, but also stress-induced vocalizations in mammals (see Kramer et al., 1998). In the guinea pig model, a selective tachykinin NK_1 receptor agonist caused vocalizations which were inhibited by tachykinin NK_1 receptor antagonists, as well as by antidepressant agents such as imipramine and fluoxetine, but not by anxiolytics like diazepam. Interestingly, MK-869 has also been reported to be an effective antidepressant in a double-blind, placebo-controlled clinical study in humans, with similar efficacy as paroxetine (Kramer et al., 1998). This in fact represents the first promising clinical trial with a NK_1 receptor antagonist on a rather large scale. The mechanism of MK-869 is different from that of clinically used antidepressant drugs and may involve the integration of emotional responses to stress by the amygdala or related brain areas.

14. Emesis

Tachykinins are localized in the brainstem not only of rodents, but also in the ferret in areas that are assumed to be involved in nausea and emesis. Ferrets provide a useful experimental model for studying emesis induced by various agents. As ferrets express the human/guinea pig subtype of tachykinin NK_1 receptors, proper compounds with tachykinin NK_1 receptor antagonism have been studied in this model (Watson et al., 1995). Centrally acting (+)-2*S*,3*S*-3-(2-methoxybenzylamino)-2-phenylpiperidine (CP 99994) and [(2-benzofuran)-CH_2OCO]-(*R*)-alpha-MeTrp-(*S*)-NHCH(CH_3)P (PD 154075) have been reported to inhibit emesis induced by apomorphine and loperimidine, two compounds that act through central mechanisms, and by peripherally acting agents such as copper sulfate and cisplatine, a cytotoxic, 'chemotherapeutic' agent (Bountra et al., 1993; Tattersall et al., 1993, 1994, 1996; Watson et al., 1995; Gonsalves et al., 1996; Rudd et al., 1996; Kris et al., 1997; Singh et al., 1997). The efficacy of particular compounds is significantly dependent on brain penetration indicating a central action of tachykinin NK_1 receptor antagonists and the need of brain penetrating compounds for putative therapeutic use (Rupniak et al., 1997). Interestingly, tachykinin NK_1 receptor antagonists act differently from 5-HT_3 receptor antagonists in a sense that the latter do not inhibit emesis elicited by central stimuli such as apomorphine (McLean, 1996). Therefore, tachykinin NK_1 receptor antagonists represent not only a new group of compounds for treatment of emesis, but may also have a wider spectrum of efficacy compared with 5-HT_3 receptor antagonists (Tavorath and Hesketh, 1996). Confirming these assumptions, very recently in a phase II clinical study with 2-(*R*)-(1-(*R*)-3, 5-bis(trifluoromethyl)phenylethoxy)-3-(*S*)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methyl morpholine (L-754,030) involving 159 patients a preven-

tion of delayed emesis after treatment with cisplatin was reported. A combination of L-754,030 with granisetron plus dexamethasone even improved the prevention of acute emesis (Navari et al., 1999).

15. Other effects of tachykinin NK_1 receptor antagonists in brain

Few additional studies provide evidence for discrete functions in brain. Intracerebroventricular injection of RP 67580 attenuates some symptoms of the responses to morphine withdrawal in rats (Maldonado et al., 1993). Furthermore, tachykinin NK_1 receptors are involved in stress-induced activation of ascending central pathways in the locus coeruleus (McLean et al., 1993). The involvement of tachykinins in central control of stress responses has been shown with tachykinin NK_1 receptor antagonists by Culman et al. (1997). Tachykinin NK_1 receptor antagonists also affect the footshock-induced sensitization of the acoustic startle response in caudate pontine reticular neurons (Krase et al., 1994) and in the facilitation of defensive rage behaviour in cats induced by stimulation of the amygdala (Shaikh et al., 1993), as revealed by using either CP 96345 or CP 99994.

Tachykinin NK_1 receptor agonists inhibit AngII-induced drinking in rats which can be reversed with a tachykinin NK_1 receptor antagonist (Polidori et al., 1998). Recently, by electrophysiological investigations, SP was found to enhance NMDA channel function in hippocampal dentate gyrus granule cells, an effect blocked by CP 99994 (Lieberman and Mody, 1998). Another compound has been found to influence circadian rhythm of locomotor activity in hamsters (Challet et al., 1998). An interesting aspect is the reduction of infarct volume in a rat model of cerebral ischemia by Yu et al. (1997), pointing to a putative potential of tachykinin NK_1 receptor antagonists in certain neurological disorders. In cat, CP 99994 has been described to be an antitussive agent with a central site of action (Bolser et al., 1997).

In conclusion, the pharmacological, behavioural and molecular investigations of tachykinin NK_1 receptors have advanced remarkably the knowledge of neuropeptide receptors and function in general, and tachykinins in particular. This knowledge has led to development of new compounds with potential clinical interest and development has reached phase II clinical studies in some examples of disturbed brain function, i.e., emesis or depression.

References

Anderson, J.J., Randall, S., Chase, T.N., 1995. The neurokinin 1 receptor antagonist CP-99,994 reduces catalepsy produced by the dopamine D_2 receptor antagonist raclopride: correlation with extracellular acetylcholine levels in striatum. J. Pharmacol. Exp. Ther. 274, 928–936.

Aubry, J.M., Lundstrom, K., Kawashima, E., Ayala, G., Schulz, P., Bartanusz, V., Kiss, J.Z., 1994. NK_1 receptor expression by cholinergic interneurones in human striatum. NeuroReport 5, 1597–1600.

Bannon, M.J., Whitty, C.J., 1995. Neurokinin receptor gene expression in substantia nigra: localization, regulation, and potential physiological significance. Can. J. Physiol. Pharmacol. 73, 866–870.

Bannon, M.J., Lee, J.M., Giraud, P., Young, A., Affolter, H.U., Bonner, T.I., 1986. Dopamine antagonist haloperidol decreases substance P, substance K, and preprotachykinin mRNA. J. Biol. Chem. 261, 6640–6642.

Bannon, M.J., Elliott, P.J., Bunney, E.B., 1987. Striatal tachykinin biosynthesis: regulation of mRNA and peptide levels by dopamine agonists and antagonists. Brain Res. 427, 31–37.

Barker, R., 1986. Substance P and Parkinson's disease: a causal relationship? J. Theor. Biol. 120, 353–362.

Barker, R., 1990. Model for basal ganglia disorders. TINS 13, 93–93.

Barker, R., 1991. Substance-P and neurodegenerative disorders—a speculative review. Neuropeptides 20, 73–78.

Barker, R., 1996. Tachykinins, neurotrophism and neurodegenerative diseases: a critical review on the possible role of tachykinins in the aetiology of CNS diseases. Rev. Neurosci. 7, 187–214.

Beaujouan, J.C., Torrens, Y., Saffroy, M., Glowinski, J., 1986. Quantitative autoradiographic analysis of the distribution of binding sites for [^{125}I]Bolton Hunter derivatives of eledoisin and substance P in the rat brain. Neuroscience 18, 857–875.

Bolser, D.C., DeGennaro, F.C., O'Reilly, S., McLeod, R.L., Hey, J.A., 1997. Central antitussive activity of the NK_1 and NK_2 tachykinin receptor antagonists, CP-99,994 and SR 48968, in the guinea-pig and cat. Br. J. Pharmacol. 121, 165–170.

Bountra, C., Bunce, K., Dale, T., Gardner, C., Jordan, C., Twissell, D., Ward, P., 1993. Anti-emetic profile of a non-peptide neurokinin NK_1 receptor antagonist, CP-99,994, in ferrets. Eur. J. Pharmacol. 249, R3–R4.

Bristow, L.J., Young, L., 1994. Chromodacryorrhea and repetitive hind paw tapping: models of peripheral and central tachykinin NK_1 receptor activation in gerbils. Eur. J. Pharmacol. 253, 245–252.

Challet, E., Naylor, E., Metzger, J.M., MacIntyre, D.E., Turek, F.W., 1998. An NK_1 receptor antagonist affects the circadian regulation of locomotor activity in golden hamsters. Brain Res. 800, 32–39.

Culman, J., Klee, S., Ohlendorf, C., Unger, T., 1997. Effect of tachykinin receptor inhibition in the brain on cardiovascular and behavioral responses to stress. J. Pharmacol. Exp. Ther. 280, 238–246.

Dam, T.V., Quirion, R., 1986. Pharmacological characterization and autoradiographic localization of substance P receptors in guinea pig brain. Peptides 7, 855–864.

Danks, J.A., Rothman, R.B., Cascieri, M.A., Chicchi, G.G., Liang, T., Herkenham, M., 1986. A comparative autoradiographic study of the distributions of substance P and eledoisin binding sites in rat brain. Brain Res. 385, 273–281.

De, F.C., Herrero, J.F., O'Brien, J.A., Palmer, J.A., Doyle, C.A., Smith, A.J., Laird, J.M., Belmonte, C., Cervero, F., Hunt, S.P., 1998. Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. Nature 392, 394–397, see comments.

Elliott, P.J., Iversen, S.D., 1986. Behavioural effects of tachykinins and related peptides. Brain Res. 381, 68–76.

Elliott, P.J., Mason, G.S., Graham, E.A., Turpin, M.P., Hagan, R.M., 1992. Modulation of the rat mesolimbic dopamine pathway by neurokinins. Behav. Brain Res. 51, 77–82.

File, S.E., 1997. Anxiolytic action of a neurokinin1 receptor antagonist in the social interaction test. Pharmacol. Biochem. Behav. 58, 747–752.

Fong, T.M., Yu, H., Strader, C.D., 1992. Molecular basis for the species selectivity of the neurokinin-1 receptor antagonist CP-96345. J. Biol. Chem. 267, 25668–25671.

Futami, T., Hatanaka, Y., Matsushita, K., Furuya, S., 1998. Expression of substance P receptor in the substantia nigra. Brain Res. Mol. Brain Res. 54, 183–198.

Garcia, M., Sakamoto, K., Shigekawa, M., Nakanishi, S., Ito, S., 1994. Multiple mechanisms of arachidonic acid release in Chinese hamster

ovary cells transfected with cDNA of substance P receptor. Biochem. Pharmacol. 48, 1735–1741.

Garret, C., Carruette, A., Fardin, V., Moussaoui, S., Peyronel, J.F., Blanchard, J.C., Laduron, P.M., 1991. Pharmacological properties of a potent and selective nonpeptide substance P antagonist. Proc. Natl. Acad. Sci. USA 88, 10208–10212.

Goldstein, D.J., Wang, O., Saper, J.R., Stoltz, R., Silberstein, S.D., Mathew, N.T., 1997. Ineffectiveness of neurokinin-1 antagonist in acute migraine: a crossover study. Cephalalgia 17, 785–790.

Gonsalves, S., Watson, J., Ashton, C., 1996. Broad spectrum antiemetic effects of CP-122,721, a tachykinin NK_1 receptor antagonist, in ferrets. Eur. J. Pharmacol. 305, 181–185.

Gorbulev, V., Akhundova, A., Luzius, H., Fahrenholz, F., 1992. Molecular cloning of substance P receptor cDNA from guinea-pig uterus. Biochim. Biophys. Acta 1131, 99–102.

Guard, S., Watson, S.P., 1991. Tachykinin receptor types: classification and membrane signalling mechanisms. Neurochem. Int. 18, 149–165.

Haverstick, D.M., Rubenstein, A., Bannon, M.J., 1989. Striatal tachykinin gene expression regulated by interaction of D-1 and D-2 dopamine receptors. J. Pharmacol. Exp. Ther. 248, 858–862.

Herkenham, M., 1987. Mismatches between neurotransmitter and receptor localizations in brain: observations and implications. Neuroscience 23, 1–38.

Hershey, A.D., Krause, J.E., 1990. Molecular characterization of a functional cDNA encoding the rat substance P receptor. Science 247, 958–962.

Hosoki, R., Yanagisawa, M., Onishi, Y., Yoshioka, K., Otsuka, M., 1998. Pharmacological profiles of new orally active nonpeptide tachykinin NK_1 receptor antagonists. Eur. J. Pharmacol. 341, 235–241.

Hua, X.Y., Saria, A., Gamse, R., Theodorsson, N.E., Brodin, E., Lundberg, J.M., 1986. Capsaicin induced release of multiple tachykinins (substance P, neurokinin A and eledoisin-like material) from guinea-pig spinal cord and ureter. Neuroscience 19, 313–319.

Humpel, C., Knaus, G.A., Auer, B., Knaus, H.G., Haring, C., Theodorsson, E., Saria, A., 1990. Effects of haloperidol and clozapine on preprotachykinin-A messenger RNA, tachykinin tissue levels, release and neurokinin-1 receptors in the striato-nigral system. Synapse 6, 1–9.

Iyengar, S., Hipskind, P.A., Gehlert, D.R., Schober, D., Lobb, K.L., Nixon, J.A., Helton, D.R., Kallman, M.J., Boucher, S., Couture, R., Li, D.L., Simmons, R.M., 1997. LY303870, a centrally active neurokinin-1 antagonist with a long duration of action. J. Pharmacol. Exp. Ther. 280, 774–785.

Jacoby, E., Boudon, A., Kucharczyk, N., Michel, A., Fauchere, J.L., 1997. A structural rationale for the design of water soluble peptide-derived neurokinin-1 antagonists. J. Recept. Signal Transduction Res. 17, 855–873.

Jensen, C.J., Gerard, N.P., Schwartz, T.W., Gether, U., 1994. The species selectivity of chemically distinct tachykinin nonpeptide antagonists is dependent on common divergent residues of the rat and human neurokinin-1 receptors. Mol. Pharmacol. 45, 294–299.

Kramer, M.S., Cutler, N., Feighner, J., Shrivastava, R., Carman, J., Sramek, J.J., Reines, S.A., Liu, G., Snavely, D., Wyatt, K.E., Hale, J.J., Mills, S.G., MacCoss, M., Swain, C.J., Harrison, T., Hill, R.G., Hefti, F., Scolnick, E.M., Cascieri, M.A., Chicchi, G.G., Sadowski, S., Williams, A.R., Hewson, L., Smith, D., Rupniak, N.M., 1998. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science 281, 1640–1645, see comments.

Krase, W., Koch, M., Schnitzler, H., 1994. Substance P is involved in the sensitization of the acoustic startle response by footshocks in rats. Behav. Brain Res. 63, 81–88.

Krause, J.E., Staveteig, P.T., Mentzer, J.N., Schmidt, S.K., Tucker, J.B., Brodbeck, R.M., Bu, J.Y., Karpitskiy, V.V., 1997. Functional expression of a novel human neurokinin-3 receptor homolog that binds [^{3}H]senktide and [^{125}I-MePhe7]neurokinin B, and is responsive to tachykinin peptide agonists. Proc. Natl. Acad. Sci. USA 94, 310–315.

Kris, M.G., Radford, J.E., Pizzo, B.A., Inabinet, R., Hesketh, A., Hesketh, P.J., 1997. Use of an NK_1 receptor antagonist to prevent delayed emesis after cisplatin. J. Natl. Cancer Inst. 89, 817–818, letter.

Kwatra, M.M., Schwinn, D.A., Schreurs, J., Blank, J.L., Kim, C.M., Benovic, J.L., Krause, J.E., Caron, M.G., Lefkowitz, R.J., 1993. The substance P receptor, which couples to Gq/11, is a substrate of beta-adrenergic receptor kinase 1 and 2. J. Biol. Chem. 268, 9161–9164.

Laufer, R., Gilon, C., Chorev, M., Selinger, Z., 1986. Characterization of a neurokinin B receptor site in rat brain using a highly selective radioligand. J. Biol. Chem. 261, 10257–10263.

Lavielle, S., Brunissen, A., Carruette, A., Garret, C., Chassaing, G., 1994. Highly potent substance P antagonists substituted with beta-phenyl-or beta-benzyl-proline at position 10. Eur. J. Pharmacol. 258, 273–276.

Lee, C.M., Campbell, N.J., Williams, B.J., Iversen, L.L., 1986. Multiple tachykinin binding sites in peripheral tissues and in brain. Eur. J. Pharmacol. 130, 209–217.

Lieberman, D.N., Mody, I., 1998. Substance P enhances NMDA channel function in hippocampal dentate gyrus granule cells. J. Neurophysiol. 80, 113–119.

Liminga, U., Gunne, L.M., 1993. Intranigral stimulation of oral movements by [pro(9)] substance-P, a neurokinin-1 receptor agonist, is enhanced in chronically neuroleptic-treated rats. Behav. Brain Res. 57, 93–99.

Longmore, J., Hill, R.G., Hargreaves, R.J., 1997. Neurokinin-receptor antagonists: pharmacological tools and therapeutic drugs. Can. J. Physiol. Pharmacol. 75, 612–621.

Lundberg, J.M., Saria, A., 1987. Polypeptide-containing neurons in airway smooth muscle. Annu. Rev. Physiol. 49, 557–572.

Lundberg, J.M., Saria, A., Brodin, E., Rosell, S., Folkers, K., 1983. A substance P antagonist inhibits vagally induced increase in vascular permeability and bronchial smooth muscle contraction in the guinea pig. Proc. Natl. Acad. Sci. USA 80, 1120–1124.

Lundberg, J.M., Saria, A., Rosell, S., Folkers, K., 1984. A substance P antagonist inhibits heat-induced oedema in the rat skin. Acta Physiol. Scand. 120, 145–146.

Macdonald, S.G., Boyd, N.D., 1989. Regulation of substance P receptor affinity by guanine nucleotide-binding proteins. J. Neurochem. 53, 264–272.

Macdonald, S.G., Dumas, J.J., Boyd, N.D., 1996. Chemical cross-linking of the substance P (NK-1) receptor to the alpha subunits of the G proteins Gq and G11. Biochemistry 35, 2909–2916.

Maggi, C.A., 1997. Tachykinins as peripheral modulators of primary afferent nerves and visceral sensitivity. Pharmacol. Res. 36, 153–169.

Maggi, C.A., Schwartz, T.W., 1997. The dual nature of the tachykinin NK_1 receptor. Trends Pharmacol. Sci. 18, 351–355.

Maggi, C.A., Giuliani, S., Santicioli, P., Regoli, D., Meli, A., 1987. Peripheral effects of neurokinins: functional evidence for the existence of multiple receptors. J. Auton. Pharmacol. 7, 11–32.

Maggi, C.A., Patacchini, R., Feng, D.M., Folkers, K., 1991. Activity of spantide I and II at various tachykinin receptors and NK_2 tachykinin receptor subtypes. Eur. J. Pharmacol. 199, 127–129.

Maggi, C.A., Patacchini, R., Rovero, P., Giachetti, A., 1993. Tachykinin receptors and tachykinin receptor antagonists. J. Auton. Pharmacol. 13, 23–93.

Malcangio, M., Bowery, N.G., 1994. Effect of the tachykinin NK_1 receptor antagonists, RP 67580 and SR 140333, on electrically-evoked substance P release from rat spinal cord. Br. J. Pharmacol. 113, 635–641.

Maldonado, R., Girdlestone, D., Roques, B.P., 1993. RP 67580, a selective antagonist of neurokinin-1 receptors, modifies some of the naloxone-precipitated morphine withdrawal signs in rats. Neurosci. Lett. 156, 135–140.

Marksteiner, J., Saria, A., Miller, C.H., Krause, J.E., 1992. Differential increases of neurokinin B- and enkephalin-like immunoreactivities and their mRNAs after chronic haloperidol treatment in the rat. Neurosci. Lett. 148, 55–59.

Marksteiner, J., Saria, A., Miller, C.H., Krause, J.E., 1993. Increased synthesis of neurokinin B and enkephalin after chronic haloperidol treatment. Regul. Pept. 46, 349–351.

McLean, S., 1996. Nonpeptide antagonists of the NK_1 tachykinin receptor. Med. Res. Rev. 16, 297–317.

McLean, S., Ganong, A., Seymour, P.A., Snider, R.M., Desai, M.C., Rosen, T., Bryce, D.K., Longo, K.P., Reynolds, L.S., Robinson, G., 1993. Pharmacology of CP-99,994; a nonpeptide antagonist of the tachykinin neurokinin-1 receptor. J. Pharmacol. Exp. Ther. 267, 472–479.

Minabe, Y., Emori, K., Toor, A., Stutzmann, G.E., Ashby, J.-C.R., 1996. The effect of the acute and chronic administration of CP 96,345, a selective neurokinin1 receptor antagonist, on midbrain dopamine neurons in the rat: a single unit, extracellular recording study. Synapse 22, 35–45.

Mitsuhashi, M., Ohashi, Y., Shichijo, S., Christian, C., Sudduth, K.J., Harrowe, G., Payan, D.G., 1992. Multiple intracellular signaling pathways of the neuropeptide substance P receptor. J. Neurosci. Res. 32, 437–443.

Mochizuki, O.N., Nakajima, Y., Nakanishi, S., Ito, S., 1994. Characterization of the substance P receptor-mediated calcium influx in cDNA transfected Chinese hamster ovary cells. A possible role of inositol 1,4,5-trisphosphate in calcium influx. J. Biol. Chem. 269, 9651–9658.

Nakajima, Y., Tsuchida, K., Negishi, M., Ito, S., Nakanishi, S., 1992. Direct linkage of three tachykinin receptors to stimulation of both phosphatidylinositol hydrolysis and cyclic AMP cascades in transfected Chinese hamster ovary cells. J. Biol. Chem. 267, 2437–2442.

Navari, R.M., Reinhardt, R.R., Gralla, R.J., Kris, M.G., Hesketh, P.J., Khojasteh, A., Kindler, H., Grote, T.H., Pendergrass, K., Grunberg, S.M., Carides, A.D., Gertz, B.J., 1999. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754,030 antiemetic trials group. New Engl. J. Med. 340, 190–195.

Otsuka, M., Yoshioka, K., 1993. Neurotransmitter functions of mammalian tachykinins. Physiol. Rev. 73, 229–308.

Phebus, L.A., Johnson, K.W., Stengel, P.W., Lobb, K.L., Nixon, J.A., Hipskind, P.A., 1997. The non-peptide NK_1 receptor antagonist LY303870 inhibits neurogenic dural inflammation in guinea pigs. Life Sci. 60, 1553–1561.

Piot, O., Betschart, J., Grall, I., Ravard, S., Garret, C., Blanchard, J.C., 1995. Comparative behavioural profile of centrally administered tachykinin NK_1, NK_2 and NK_3 receptor agonists in the guinea-pig. Br. J. Pharmacol. 116, 2496–2502.

Polidori, C., Ciccocioppo, R., De, C.G., Massi, M., 1998. Further evidence that central tachykinin NK_1 receptors mediate the inhibitory effect of tachykinins on angiotensin-induced drinking in rats. Peptides 19, 149–155.

Pradier, L., Habert, O.E., Emile, L., Le, G.J., Loquet, I., Bock, M.D., Clot, J., Mercken, L., Fardin, V., Garret, C., 1995. Molecular determinants of the species selectivity of neurokinin type 1 receptor antagonists. Mol. Pharmacol. 47, 314–321.

Quartara, L., Maggi, C.A., 1997. The tachykinin NK1 receptor: Part I. ligands and mechanisms of cellular activation. Neuropeptides 31, 537–563.

Quartara, L., Maggi, C.A., 1998. The tachykinin NK1 receptor: Part II. Distribution and pathophysiological roles. Neuropeptides 32, 1–49.

Radhakrishnan, V., Iyengar, S., Henry, J.L., 1998. The nonpeptide NK_1 receptor antagonists LY303870 and LY306740 block the responses of spinal dorsal horn neurons to substance P and to peripheral noxious stimuli. Neuroscience 83, 1251–1260.

Regoli, D., Nantel, F., 1991. Pharmacology of neurokinin receptors. Biopolymers 31, 777–783.

Regoli, D., Boudon, A., Fauchere, J.L., 1994. Receptors and antagonists for substance P and related peptides. Pharmacol. Rev. 46, 551–599.

Regoli, D., Drapeau, G., Dion, S., Couture, R., 1988. New selective agonists for neurokinin receptors: pharmacological tools for receptor characterization. Trends Pharmacol. Sci. 9, 290–295.

Regoli, D., Drapeau, G., Dion, S., D'Orleans, J.P., 1987. Pharmacological receptors for substance P and neurokinins. Life Sci. 40, 109–117.

Regoli, D., Drapeau, G., Dion, S., D'Orleans, J.P., 1989. Receptors for substance P and related neurokinins. Pharmacology 38, 1–15.

Rudd, J.A., Jordan, C.C., Naylor, R.J., 1996. The action of the NK_1 tachykinin receptor antagonist, CP 99,994, in antagonizing the acute and delayed emesis induced by cisplatin in the ferret. Br. J. Pharmacol. 119, 931–936.

Rupniak, N.M., Tattersall, F.D., Williams, A.R., Rycroft, W., Carlson, E.J., Cascieri, M.A., Sadowski, S., Ber, E., Hale, J.J., Mills, S.G., MacCoss, M., Seward, E., Huscroft, I., Owen, S., Swain, C.J., Hill, R.G., Hargreaves, R.J., 1997. In vitro and in vivo predictors of the anti-emetic activity of tachykinin NK_1 receptor antagonists. Eur. J. Pharmacol. 326, 201–209.

Sachais, B.S., Krause, J.E., 1994. Both extracellular and transmembrane residues contribute to the species selectivity of the neurokinin-1 receptor antagonist WIN 51708. Mol. Pharmacol. 46, 122–128.

Sachais, B.S., Snider, R.M., Lowe, J.A., Krause, J.E., 1993. Molecular basis for the species selectivity of the substance P antagonist CP-96,345. J. Biol. Chem. 268, 2319–2323.

Saffroy, M., Beaujouan, J.C., Torrens, Y., Besseyre, J., Bergstrom, L., Glowinski, J., 1988. Localization of tachykinin binding sites (NK_1, NK_2, NK_3 ligands) in the rat brain. Peptides 9, 227–241.

Saria, A., 1984. Substance P in sensory nerve fibres contributes to the development of oedema in the rat hind paw after thermal injury. Br. J. Pharmacol. 82, 217–222.

Saria, A., Gamse, R., Petermann, J., Fischer, J.A., Theodorsson, N.E., Lundberg, J.M., 1986. Simultaneous release of several tachykinins and calcitonin gene-related peptide from rat spinal cord slices. Neurosci. Lett. 63, 310–314.

Saria, A., Troger, J., Zernig, G., 1993. Different behavioral profiles of the non-peptide substance P (NK_1) antagonists CP-96,345 and RP 67580. Regul. Pept. 46, 346–348.

Seabrook, G.R., Fong, T.M., 1993. Thapsigargin blocks the mobilisation of intracellular calcium caused by activation of human NK_1 (long) receptors expressed in Chinese hamster ovary cells. Neurosci. Lett. 152, 9–12.

Shaikh, M.B., Steinberg, A., Siegel, A., 1993. Evidence that substance P is utilized in medial amygdaloid facilitation of defensive rage behavior in the cat. Brain Res. 625, 283–294.

Shigemoto, R., Nakaya, Y., Nomura, S., Ogawa-Meguro, R., Ohishi, H., Kaneko, T., Nakanishi, S., Mizuno, N., 1993. Immunocytochemical localization of rat substance P receptor in the striatum. Neurosci. Lett. 153, 157–160.

Singh, L., Field, M.J., Hughes, J., Kuo, B.S., Suman, C.N., Tuladhar, B.R., Wright, D.S., Naylor, R.J., 1997. The tachykinin NK_1 receptor antagonist PD 154075 blocks cisplatin-induced delayed emesis in the ferret. Eur. J. Pharmacol. 321, 209–216.

Sivam, S.P., Krause, J.E., 1992. Tachykinin systems in the spinal cord and basal ganglia: influence of neonatal capsaicin treatment or dopaminergic intervention on levels of peptides, substance P-encoding mRNAs, and substance P receptor mRNA. J. Neurochem. 59, 2278–2284.

Sivam, S.P., Krause, J.E., Takeuchi, K., Li, S., McGinty, J.F., Hong, J.S., 1989. Lithium increases rat striatal beta- and gamma-preprotachykinin messenger RNAs. J. Pharmacol. Exp. Ther. 248, 1297–1301.

Snider, R.M., Constantine, J.W., Lowe, J.A., Longo, K.P., Lebel, W.S., Woody, H.A., Drozda, S.E., Desai, M.C., Vinick, F.J., Spencer, R.W., 1991. A potent nonpeptide antagonist of the substance P (NK_1) receptor. Science 251, 435–437.

Stoessl, A.J., Brackstone, M., Rajakumar, N., Gibson, C.J., 1995. Pharmacological characterization of grooming induced by a selective NK_1 tachykinin receptor agonist. Brain Res. 700, 115–120.

Sundelin, J.B., Provvedini, D.M., Wahlestedt, C.R., Laurell, H., Pohl, J.S., Peterson, P.A., 1992. Molecular cloning of the murine substance K and substance P receptor genes. Eur. J. Biochem. 203, 625–631.

Takeda, Y., Blount, P., Sachais, B.S., Hershey, A.D., Raddatz, R., Krause, J.E., 1992. Ligand binding kinetics of substance P and neurokinin A receptors stably expressed in Chinese hamster ovary cells and evidence for differential stimulation of inositol 1,4,5-trisphosphate and cyclic AMP second messenger responses. J. Neurochem. 59, 740–745.

Tattersall, F.D., Rycroft, W., Hargreaves, R.J., Hill, R.G., 1993. The tachykinin NK_1 receptor antagonist CP-99,994 attenuates cisplatin induced emesis in the ferret. Eur. J. Pharmacol. 250, R5–R6.

Tattersall, F.D., Rycroft, W., Hill, R.G., Hargreaves, R.J., 1994. Enantioselective inhibition of apomorphine-induced emesis in the ferret by the neurokinin1 receptor antagonist CP-99,994. Neuropharmacology 33, 259–260.

Tattersall, F.D., Rycroft, W., Francis, B., Pearce, D., Merchant, K., MacLeod, A.M., Ladduwahetty, T., Keown, L., Swain, C., Baker, R., Cascieri, M., Ber, E., Metzger, J., MacIntyre, D.E., Hill, R.G., Hargreaves, R.J., 1996. Tachykinin NK_1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. Neuropharmacology 35, 1121–1129.

Tavorath, R., Hesketh, P.J., 1996. Drug treatment of chemotherapy-induced delayed emesis. Drugs 52, 639–648.

Teixeira, R.M., Santos, A.R., Ribeiro, S.J., Calixto, J.B., Rae, G.A., De, L.T., 1996. Effects of central administration of tachykinin receptor agonists and antagonists on plus-maze behavior in mice. Eur. J. Pharmacol. 311, 7–14.

Walpole, C., Ko, S.Y., Brown, M., Beattie, D., Campbell, E., Dickenson, F., Ewan, S., Hughes, G.A., Lemaire, M., Lerpiniere, J., Patel, S., Urban, L., 1998a. 2-Nitrophenylcarbamoyl-(*S*)-prolyl-(*S*)-3-(2-naphthyl)alanyl-*N*-benzyl-*N*-methylamide (SDZ NKT 343), a potent human NK_1 tachykinin receptor antagonist with good oral analgesic activity in chronic pain models. J. Med. Chem. 41, 3159–3173.

Walpole, C.S., Brown, M.C., James, I.F., Campbell, E.A., McIntyre, P., Docherty, R., Ko, S., Hedley, L., Ewan, S., Buchheit, K.H., Urban, L.A., 1998b. Comparative, general pharmacology of SDZ NKT 343, a novel, selective NK_1 receptor antagonist. Br. J. Pharmacol. 124, 83–92.

Watson, J.W., Gonsalves, S.F., Fossa, A.A., McLean, S., Seeger, T., Obach, S., Andrews, P.L., 1995. The anti-emetic effects of CP-99,994 in the ferret and the dog: role of the NK1 receptor. Br. J. Pharmacol. 115, 84–94.

Whitty, C.J., Walker, P.D., Goebel, D.J., Poosch, M.S., Bannon, M.J., 1995. Quantitation, cellular localization and regulation of neurokinin receptor gene expression within the rat substantia nigra. Neuroscience 64, 419–425.

Whitty, C.J., Paul, M.A., Bannon, M.J., 1997. Neurokinin receptor mRNA localization in human midbrain dopamine neurons. J. Comp. Neurol. 382, 394–400.

Yokota, Y., Sasai, Y., Tanaka, K., Fujiwara, T., Tsuchida, K., 1989. Molecular characterization of a functional cDNA for rat substance P receptor. J. Biol. Chem. 264, 17649–17652.

Yu, Z., Cheng, G., Huang, X., Li, K., Cao, X., 1997. Neurokinin-1 receptor antagonist SR140333: a novel type of drug to treat cerebral ischemia. NeuroReport 8, 2117–2119.

Zernig, G., Dietrich, H., Maggi, C.A., Saria, A., 1992. The substance P (NK_1) receptor antagonist (±)-CP-96,345 causes sedation and motor impairment in Swiss albino mice in the black-and-white box behavioral paradigm. Neurosci. Lett. 143, 169–172.

Zernig, G., Troger, J., Saria, A., 1993. Different behavioral profiles of the non-peptide substance P (NK_1) antagonists CP-96,345 and RP 67580 in Swiss albino mice in the black-and-white box. Neurosci. Lett. 151, 64–66.