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SUBSTANCE P AND RELATED TACHYKININS

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Substance P belongs to a family of neuropeptides known as tachykinins that share the common C-terminal sequence: Phe-X-Gly-Leu-Met-NH2. The three most common tachykinins are substance P, neurokinin A (NKA), and neurokinin B (NKB); their biologic actions are mediated through specific cell-surface receptors designated NK_1, NK_2, and NK_3, with substance P the preferred agonist for NK_1 receptors, NKA for NK_2 receptors, and NKB for NK_3 receptors.

Preclinical studies with substance P antagonists have been complicated not only by phylogenetic differences in central nervous system (CNS) localization of tachykinin receptors, but also by species variants in NK_1 receptor pharmacology. This situation greatly complicates preclinical evaluation of selective substance P receptor antagonists because most of these have only low affinity for the rat receptor, which is the most commonly used preclinical species. Substance P and the NK_1 receptor have a widespread distribution in the brain and are found in brain regions that regulate emotion (e.g., amygdala, periaqueductal gray, hypothalamus). They are also found in close association with 5-hydroxytryptamine (5-HT) and norepinephrine-containing neurons that are targeted by the currently used antidepressant drugs.

The effects of substance P antagonists in preclinical assays for analgesic, antiemetic, antipsychotic, anxiolytic, and antidepressant drugs is reviewed. The process of elucidating the clinical uses of substance P antagonists raises certain fundamental issues that will apply to other novel neurotransmitter ligands in future. The difficulty of predicting clinical efficacy from preclinical data, and of testing novel therapeutic drugs in patients with psychiatric disorders, is discussed.

Substance P, NKA, and NKB are related neuropeptides that are widely distributed in the peripheral nervous system and the CNS. With the development of selective nonpeptide receptor antagonists, it has become possible to investigate the physiologic roles of these peptides and to explore their use as novel treatments for neurologic and psychiatric disorders. Because the substance P–preferring NK_1 receptor is the predominant tachykinin receptor expressed in the human brain, most compounds that have been developed for clinical use are substance P–preferring (NK_1) receptor antagonists.

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TACHYKININ FAMILY OF PEPTIDES

Substance P belongs to a family of neuropeptides known as tachykinins that share the common C-terminal sequence: Phe-X-Gly-Leu-Met-NH_2. Two other mammalian tachykinins are NKA and NKB (Table 13.1). Their biologic actions are mediated through specific G-protein–coupled neurokinin receptors designated NK_1, NK_2, and NK_3, with substance P the preferred agonist for NK_1 receptors, NKA for NK_2 receptors, and NKB for NK_3 receptors. However, the receptor selectivity of these peptides is relatively poor, and it is possible that their actions could be mediated by activation of their less preferred receptors. Indeed, this possibility is suggested by the mismatch between tachykinin-containing neurons and fibers and their corresponding receptor that is seen in certain brain regions. This is particularly apparent in the case of NKA, because NK_2 receptor expression appears to be extremely low in the adult mammalian brain (1).

Substance P was originally discovered in 1931 by von Euler and Gaddum as a tissue extract that caused intestinal contraction *in vitro;* its biologic actions and tissue distribution were further investigated over subsequent decades. NKA (previously known as substance K or neuromedin L) and NKB (originally known as neuromedin K), were isolated from porcine spinal cord in 1983 and were also found to stimulate intestinal contraction (2). Substance P and NKA are produced from a polyprotein precursor after differential splicing of a single precursor gene, preprotachykinin

TABLE 13.1. MAMMALIAN TACHYKININS

Substance P	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-MetNH_2
Neurokinin A	His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-MetNH_2
Neurokinin B	Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-MetNH_2

A (3). NKB is produced from a distinct precursor protein encoded by preprotachykinin B (4).

The existence of several neurokinin receptors was originally suggested by the differential contractile responses elicited in various tissues by mammalian and nonmammalian tachykinins (5). Subsequently, specific binding sites labeled by Bolton Hunter substance P, NKA, and eledoisin were identified in the CNS (6), a finding suggesting that at least three receptors mediated the actions of tachykinins. This was confirmed by cloning of three distinct functional cDNA constructs corresponding to NK_1, NK_2, and NK_3 receptor, which preferentially bound substance P, NKA, and NKB, respectively (7–9). However, the endogenous neurokinins exhibit a high degree of cross-reactivity with these tachykinin receptors.

SPECIES DIFFERENCES IN THE DISTRIBUTION OF NEUROKININS AND THEIR RECEPTORS IN THE NERVOUS SYSTEM

The substance P–preferring NK_1 receptor has attracted most interest as a CNS drug target because it is the predominant tachykinin receptor expressed in the human brain, whereas NK_2 and NK_3 receptor expression is extremely low or absent (10–12). Therefore, it appears that the central actions of all tachykinins may be mediated predominantly through the NK_1 receptor in humans. However, understanding the role of substance P in the brain has been greatly complicated by marked differences in the distribution of tachykinin receptor subtypes in rodent species that are normally used for such studies. For example, in the rat and guinea pig brain, both NK_1 and NK_3 receptors are expressed (10), findings suggesting that the CNS functions mediated by NK_1 receptors in the human brain may be subserved by NK_1 and/or NK_3 receptors in rodents. NK_2 receptors appear to be absent in the adult mammalian brain of all species examined (10). For these reasons, interpretation of the effects of selective tachykinin receptor antagonists in preclinical assays requires great caution. If such compounds either succeed or fail to exhibit activity in rodent assays for psychiatric and neurologic disorders, this may merely reflect different roles of tachykinin receptors in rodent versus human brain. Hence there is a risk of both false-positive and false-negative extrapolations from preclinical species to humans.

Substance P is widely distributed throughout the CNS and in primary sensory neurons. The demonstration of substance P immunoreactivity in the cell bodies of dorsal root ganglia, in sensory nerve fibers, and in the dorsal horn of the spinal cord led to early speculation that substance P is involved in pain perception (13). Substance P and the NK_1 receptor have a widespread distribution in the brain and are found in brain regions that regulate emotion (e.g., amygdala, periaqueductal gray, hypothalamus) (14,15). They are also found in close association with major catecholamine-containing nuclei, including the substantia nigra and the nucleus tractus solitarius (16), as well as with 5-HT- and norepinephrine-containing neurons that are targeted by currently used antidepressant drugs. NKA and NKB are also expressed in varying ratios in the CNS and spinal cord (17,18) and in the rodent (but not human) brain, and NK_3 receptors and mRNA have also been demonstrated in various regions, including the substantia nigra, raphe nuclei, and locus ceruleus (19–21).

An interesting aspect of the neuroanatomic localization of substance P is that that it is coexpressed with 5-HT in approximately 50% of ascending dorsal raphe neurons in the primate brain (22,23). In contrast, coexpression of substance P and 5-HT in ascending raphe neurons is not seen in the rat brain (24). These findings provide further illustrations of the marked species differences in the neuroanatomy, and possibly physiology, of neurokinin systems. The functional significance of substance P and 5-HT coexpression in the human brain is not known, but it suggests that both neurotransmitters may be coreleased in certain brain regions receiving terminal innervation.

Other evidence suggests that substance P and NKB may also modulate ascending norepinephrine systems. NK_1 receptors (25) have been shown to be expressed on tyrosine hydroxylase–positive cell bodies in the rat locus ceruleus, and both substance P and senktide (a selective NK_3 receptor agonist) excite the firing of locus ceruleus neurons in rats and guinea pigs (26,27).

PHYLOGENETIC DIFFERENCES IN TACHYKININ RECEPTOR PHARMACOLOGY

Preclinical studies with NK_1 receptor antagonists have also been complicated by species variants in NK_1 receptor pharmacology (28,29). Compounds such as CP-96,345 were found have high (nM) affinity for the NK_1 receptor expressed in human, gerbil, rabbit, guinea pig, cat, and monkey brain, but they had considerably lower affinity for the mouse and rat NK_1 receptor. Subsequent mutation analysis revealed that subtle differences in the amino acid sequence between the human and the rat NK_1 receptor dramatically alter antagonist binding affinity (30). This feature has greatly hindered preclinical evaluation of high-affinity human NK_1 receptor antagonists because most of these have considerably lower affinity for the rat receptor, the most

TABLE 13.2. SPECIES VARIANTS IN NK_1 RECEPTOR PHARMACOLOGY IC_{50} FOR INHIBITION OF [^{125}I]SP BINDING (nM)

Compound	Human	Gerbil	Guinea Pig	Rat
L-733060	0.87	0.36	0.3	550
L-760735	0.3	0.5	0.34	10
SR140333	0.04	—	—	0.2
GR205171	0.08	0.06	0.09	1.4

From G. Chicchi and M.A. Cascieri, unpublished observations.

commonly used preclinical species (Table 13.2). A few compounds have high affinity for the rat receptor (e.g., SR140333), but their utility for *in vivo* studies may be severely limited by poor brain penetration (31). Although these difficulties may be overcome by administering high doses of NK_1 receptor antagonists to rats, unspecific pharmacologic effects are then frequently encountered, mostly attributable to ion channel blockade. It has therefore been necessary to examine the preclinical pharmacology of these compounds in species with humanlike NK_1 receptor pharmacology (gerbils, guinea pigs, ferrets, hamsters) whenever possible. Pharmacologic differences among human, guinea pig, and rat NK_3 receptors also exist (32).

POTENTIAL FOR USE OF TACHYKININ RECEPTOR ANTAGONISTS TO TREAT PSYCHIATRIC AND NEUROLOGIC DISORDERS

The distribution of neurokinins in the central and peripheral nervous system has generated much speculation about the potential therapeutic uses of selective tachykinin receptor antagonists. The major hypotheses that are supported by preclinical data and have been investigated in clinical trials are considered here. Numerous clinical trials have now been conducted with NK_1 receptor antagonists to define their therapeutic potential in psychiatric and neurologic disorders. In all these studies, the compounds have been extremely well tolerated, with no significant side effects. There are as yet no reports of clinical trials with NK_2 or NK_3 receptor antagonists in patients with CNS disorders.

Pain

Radioligand-binding studies confirm the expression of tachykinin NK_1 and NK_3 (but not NK_2) receptors in the dorsal horn of the spinal cord (33–35). A role of spinal substance P and NKA in nociception is suggested by the reduction in response thresholds to noxious stimuli by central administration of NK_1 and NK_2 (but not NK_3) agonists (36–38). Based on these neuroanatomic and functional studies, it was anticipated that NK_1, and possibly NK_2, receptor antagonists could be developed as analgesic drugs.

Electrophysiologic studies on anesthetized or decerebrate animals provide evidence of potent and selective inhibition of facilitated nociceptive spinal reflexes by NK_1 receptor antagonists. Responses of dorsal horn neurons to noxious or repetitive electrical stimulation of a peripheral nerve was blocked by CP-96,345 (39); NK_1 receptor antagonists also blocked the flexor reflex facilitation produced by C-fiber–conditioning stimulation, but they did not affect protective nociceptive reflexes (40,41). NK_1 receptor antagonists have also been shown to inhibit the late-phase response to formalin in gerbils (42), to inhibit carrageenan and Freund adjuvant–induced hyperalgesia in guinea pigs (J. Webb, S. Boyce, and N. Rupniak, unpublished observations; 43), and to attenuate peripheral neuropathy in rats and guinea pigs (43,44). Overall, the profile of activity of NK_1 receptor antagonists in a range of assays is comparable to that seen with clinically used analgesic agents such as indomethacin (Table 13.3).

The first clinical trials with NK_1 receptor antagonists were conducted in patients with various pain conditions. These trials uniformly failed to confirm the analgesic efficacy of these compounds in humans and are reviewed in detail elsewhere (45,46). The patient populations and compounds examined included the following: peripheral neuropathy, in which CP-99,994 had no analgesic effect (47); molar extraction, in which MK-869 was ineffective (48); and postherpetic neuralgia, in which MK-869 was ineffective (49). Further unpublished studies with other compounds support these conclusions. Thus, clinical studies to date indicate that NK_1 receptor antagonists do not have major potential as analgesics.

Less is known about the profile of NK_2 receptor antagonists in nociception assays. The NK_2 antagonist MEN 10207 completely blocked both facilitation and protective nociceptive reflex responses (40), and SR48968 reduced responses to both noxious and innocuous pressure applied to

TABLE 13.3. PRECLINICAL EVIDENCE OF AN ANALGESIC PROFILE OF NK_1 RECEPTOR ANTAGONISTS

Assay	Morphine	Indomethacin	NK_1 Antagonist
Tail flick/hot plate	√	X	X
Paw pressure	√	X	X
Writhing	√	√	√
Formalin paw	√	√	√
Carrageenan paw	√	√	√
Nerve injury	√	X	√
CFA arthritis	√	√	√
Facilitated spinal reflex	√	√	√

the knee joint (50). In conscious rats, Sluka et al. found that pretreatment with SR48968 prevented the induction of hyperalgesia induced by intraarticular injection of kaolin and carrageenan (51), but it was not effective after hyperalgesia had been established.

Migraine

The vasculature of meningeal tissues such as the dura mater is densely innervated by nociceptive sensory afferents that run in the trigeminal nerve and contain substance P and other neuropeptides. The release of neuropeptides from these sensory fibers during a migraine attack is thought to cause neurogenic inflammation within the meninges and activation of nociceptive afferents projecting to the trigeminal nucleus caudalis (52). In rats, antidromic stimulation of the trigeminal nerve increases vascular permeability and causes plasma protein extravasation in the meninges that is inhibited by NK_1 receptor antagonists (53). These findings suggest that if meningeal plasma extravasation and inflammation of the meninges is involved in the pathogenesis of migraine, then NK_1 receptor antagonists should provide an effective antimigraine therapy. In addition, because of their potential analgesic activity, CNS-penetrant NK_1 antagonists may also be able to alleviate headache by preventing activation of sensory neurons in the trigeminal nucleus caudalis. However, this hypothesis was not confirmed in clinical trials in patients with migraine, in whom neither LY 303870 (54) nor GR205171 (55) gave headache relief.

Emesis

Substance P is present in the nucleus tractus solitarius and the area postrema (56), regions implicated in the control of emesis. Local application of substance P in the area postrema causes retching in ferrets (57), a finding suggesting that NK_1 receptor antagonists may be antiemetic. Consistent with this proposal, these compounds have emerged as an important new class of antiemetics in preclinical studies using ferrets. CP-99,994 completely abolished cisplatin-induced retching and vomiting and exhibited broad-spectrum activity against peripheral and centrally acting emetogens (58–60). Importantly, CP-99,994 markedly attenuated both acute and delayed emesis induced by cisplatin, a profile that distinguishes NK_1 receptor antagonists from established antiemetics (61, 62). The ability of CP-99,994 to block both peripherally and centrally acting emetogens and the demonstration that direct injection of CP-99,994 into the region of the nucleus tractus solitarius inhibited cisplatin-induced emesis in ferrets (63) suggest that the antiemetic activity of NK_1 antagonists is centrally mediated. This proposal was confirmed by the use of a poorly brain-penetrant quaternary NK_1 receptor antagonist, L-743,310, which prevented cisplatin-induced retching in ferrets when it was infused directly into the CNS, but not systemically (64).

Evaluation of NK_1 receptor antagonists as antiemetics in patients has produced encouraging results. Three independent trials have confirmed that CP-122,721 (65), CJ-11974 (66), and MK-869 (67) are extremely effective in the prevention of acute and delayed emesis after cisplatin chemotherapy. CP-122,721 was also effective in preventing postoperative nausea and vomiting after gynecologic surgery (68), a finding suggesting the utility of NK_1 receptor antagonists as broad-spectrum antiemetics in humans. There are no published studies examining the effects of selective NK_2 and NK_3 receptor agonists and antagonists on emesis.

Schizophrenia

A rationale that NK_1 receptor antagonists may be useful as antipsychotic drugs has been built on evidence that substance P modulates the activity of the mesolimbic dopamine system through which established antipsychotic drugs are thought to act. Substance P–containing fibers have been shown to make synaptic contact with tyrosine hydroxylase–positive neurons in the ventral tegmental area (VTA) from which the mesolimbic dopamine projection arises (69). Infusion of substance P agonists into the VTA stimulates locomotor activity in rats, an effect attributed to the activation of dopamine neurons because this is accompanied by an increase in dopamine turnover in the terminal projection area (nucleus accumbens) (70). Consistent with this interpretation, the locomotor hyperactivity and changes in accumbens cell firing induced by intra-VTA infusion of substance P were blocked by the dopamine receptor antagonist haloperidol, an antipsychotic drug (71).

The ability of a monoclonal antibody to substance P, injected into the nucleus accumbens, to attenuate the locomotor response to amphetamine (72) was consistent with the proposal that endogenous substance P modulates the release of dopamine in the mesolimbic system. A subsequent study appeared to support this interpretation because the NK_1 receptor antagonist CP-96,345 reduced the firing of cells in the VTA in rats (73). However, other studies with NK_1 receptor antagonists are not consistent with these findings. Surprisingly, intra-VTA coinfusion of CP-96,345 was unable to block substance P agonist–induced locomotor activation in rats (71), and amphetamine-induced hyperactivity in guinea pigs was not selectively inhibited by CP-99,994.

A possible explanation for the lack of effect of NK_1 receptor antagonists in these studies is that the effects of substance P in the rodent VTA may be mediated by stimulation of NK_3, rather than NK_1, receptors, as is suggested by anatomic (19), electrophysiologic (74), and behavioral (75) evidence. Intra-VTA application of the NK_3 receptor agonist senktide was shown to enhance markedly the extracellular concentration of dopamine in the nucleus accumbens and

prefrontal cortex of anesthetized guinea pigs, and this was blocked by the selective NK_3 receptor antagonist SR142801 (76). SR142801 (but not the NK_1 receptor antagonist GR205171 or the NK_2 antagonist SR144190) was able to antagonize the increase in neuronal activity caused by acute administration of haloperidol in guinea pigs (77), a finding suggesting that NK_3 receptors play a key role in regulating midbrain dopamine neurons in this species. Preliminary findings from an exploratory trial with MK-869 in patients with schizophrenia indicated that this compound did not ameliorate the core symptoms of acute psychosis (46).

Anxiety and Depression

Substance P and its preferred NK_1 receptor are highly expressed in brain regions that are critical for the regulation of emotion and neurochemical responses to stress (14,15, 24). Direct central injection of substance P agonists produces a range of fear-related behaviors and defensive cardiovascular changes in animals (78–81). Neurochemical studies have revealed rapid reductions in substance P content in the mesolimbic system, hippocampus, septum, periaqueductal gray, and hypothalamus of rats after inescapable footshock (82,83) and immobilization stress (84). These findings indicate that activation of central substance P pathways occurs in response to noxious or aversive stimulation and suggest that NK_1 receptor antagonists may have anxiolytic or antidepressant-like properties.

Substance P antagonists are capable of attenuating psychological stress responses in paradigms using neurochemical and behavioral endpoints. This was first suggested by the demonstration that intra-VTA injection of a monoclonal antibody to substance P prevented stress-induced activation of mesocortical dopamine neurons (85). More recently, the NK_1 receptor antagonist GR205171 was shown to inhibit the stress-induced elevation in the dopamine metabolite DOPAC in the frontal cortex (86). Certain chemically diverse NK_1 receptor antagonists have also shown activity in a range of assays for anxiolytic and antidepressant drugs after intracerebral or systemic administration. One of the earliest reported studies demonstrated a direct substance P–ergic projection from the medial amygdala to the medial hypothalamus that regulates the expression of defensive rage in cats. Either systemic or intrahypothalamic injection of CP-96,345 inhibited amygdaloid facilitation of defensive rage (87). A second study examined the role of NK_1 receptors in the caudal pontine reticular nucleus and showed that injection of CP-96,345 or CP-99,994 into this region blocked potentiation of the acoustic startle response by footshock in rats (88). In the resident-intruder paradigm, L-760,735 reduced aggression in singly housed hamsters in a dose-dependent manner resembling the effect of fluoxetine (J. Webb, E. Carlson, N. Rupniak, unpublished observations) (Fig. 13.1). CGP 49823 has been reported to be active in the rat social interaction test for anxiolytic activity (89,90) and the forced swim test for antidepressant drugs (89). In guinea pig pups, the vocalization response elicited by maternal separation is inhibited by brain-penetrant NK_1 receptor antagonists (L-773,060, L-760,735, GR205171), a property also seen with clinically used antidepressant and anxiolytic drugs (91,92). The amygdala is a potential site of action for this effect of NK_1 receptor antagonists because separation stress caused internalization of NK_1 receptors (reflecting the release of substance P) in this brain region (91,93), and intraamygdala injection of L-760735 attenuated the neonatal vocalizations (93). Further evidence for an antidepressant-like preclinical profile of substance P antagonists is suggested by preliminary findings with L-733,060, which was active in the learned helplessness paradigm in rats (94), despite having only low affinity for the rat NK_1 receptor. These findings are summarized in Table 13.4.

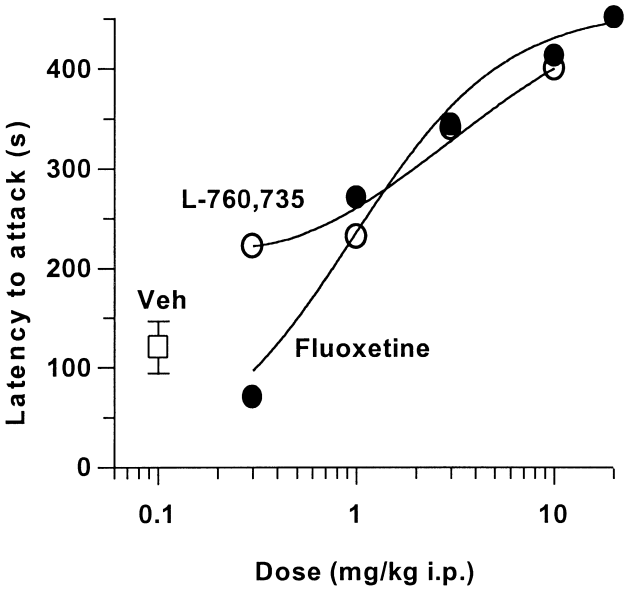

FIGURE 13.1. Activity of L-760,735 in the hamster resident-intruder test. The subjects were individually housed adult male hamsters. On test days, both resident and intruder hamsters were dosed with the same drug and were returned to their own cages for 30 minutes before testing. Pretreatment with either fluoxetine (0.3 to 30 mg/kg intraperitoneally) or the selective NK_1 receptor antagonist L-760735 (0.3 to 10 mg/kg intraperitoneally) caused a dose-dependent increase in the latency to initiate an aggressive encounter.

The NK_2 receptor antagonists SR48968, GR100679, and GR159897 have been reported to exhibit anxiolytic-like effects in several preclinical assays (mouse light-dark box, rat social interaction test, rat elevated plus maze, and marmoset threat test) (95–97). However, these compounds were reported to be extremely potent, and the micrograms per kilogram anxiolytic dose range was considerably lower

TABLE 13.4. PRECLINICAL EVIDENCE OF AN ANTIDEPRESSANT AND ANXIOLYTIC-LIKE PROFILE OF NK_1 RECEPTOR ANTAGONISTS

Assay	Species	BZ Anxiolytics	SSRI/TCA	NK_1 Antagonist
Neonatal vocalization	Guinea pig	√	√	√
Aggression	Hamster	√	√	√
Learned helpessness	Rat		√	√
Forced swim	Rat	X	√	√
Shock-potentiated startle	Rat	√		√
Social interaction	Rat	√		√

BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

than that required to block NK_2 agonist–mediated effects in peripheral tissues (mg/kg dose range) (98,99). A second difficulty concerns the failure to establish convincing expression of NK_2 receptors in the adult rat brain (100).

In rodents, there is evidence that NK_3 receptors are able to modulate monoaminergic neurotransmission. Because the clinical efficacy of currently used antidepressant drugs is ascribed to their ability to increase the synaptic availability of 5-HT and norepinephrine, modulation of these systems by NK_3 receptor ligands may suggest an antidepressant-like profile. The ability of central infusion of senktide to elicit a 5-HT behavioral syndrome (101) and to increase the release of norepinephrine in brain (27) indicates that monoamine systems can be activated by NK_3 receptor agonists. The ability of senktide to increase locus ceruleus firing, to increase norepinephrine release, and to decrease locomotor activity in animals was blocked by the selective NK_3 receptor antagonist SR142801 (101). These actions are not clearly indicative of an antidepressant-like profile of NK_3 receptor antagonists, and the low abundance of these receptors in human brain suggests that, like NK_2 receptor antagonists, NK_3 antagonists are less attractive candidates for clinical development in psychiatry than NK_1 receptor antagonists.

There is currently only one published study in which a tachykinin antagonist has been examined in patients with depression. The clinical efficacy of the NK_1 receptor antagonist MK-869 was comparable to that of paroxetine in outpatients with major depressive disorder and moderately high anxiety. As in other clinical trials, MK-869 was extremely well tolerated (94). Further studies are currently in progress with this and other NK_1 receptor antagonists in patients with depression and anxiety disorders.

CONCLUSIONS AND IMPLICATIONS FOR FUTURE STUDIES OF NEUROKININ ANTAGONISTS IN PSYCHIATRIC AND NEUROLOGIC DISORDERS

The process of elucidating the potential clinical uses of tachykinin receptor antagonists raises several fundamental issues that will apply to other novel neurotransmitter ligands in the future. Preclinical studies have suggested therapeutic potential of neurokinin antagonists in certain neurologic and psychiatric disorders, including migraine, pain, schizophrenia, anxiety, and depression. Of these, antagonists of tachykinin NK_1 receptors are the most attractive agents because this is the predominant receptor expressed in the human brain. However, expectations have been only partially fulfilled in clinical trials, and although preliminary findings suggest efficacy of NK_1 receptor antagonists in the control of emesis and depression, these compounds do not appear to possess analgesic or antipsychotic activity. It was not possible to predict this outcome from preclinical evidence, in which interpretation was complicated by species variants in tachykinin receptor pharmacology and possibly physiology, and this was coupled with uncertainty about whether relevant aspects of human disease can be accurately modeled in animals.

This chapter has focused on the intricacies of prioritizing efforts to identify the therapeutic uses of neurokinin antagonists for CNS disorders. However, there are many other potential uses for NK_1, NK_2, and NK_3 antagonists that have not yet been fully explored. These include inflammatory diseases such as cystitis and inflammatory bowel disease, asthma, cancer, glaucoma, ocular hypotension, cardiac disorders, and psoriasis.

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