In the 1960s, the first tricyclic antidepressant drugs were found to act by blocking the reuptake of the classical neurotransmitters serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE). Since then, these two monoamine neurotransmitters have been the focus of antidepressant drug research and the most common pathophysiological concepts of major depression are based on this profile of antidepressant action. Increasing knowledge has indicated that the modulation of monoamines is not the only mechanism for antidepressant actions. Neuropeptides, which are colocalized with monoamines, could also be involved in the pathophysiology of depression. Substance P (SP), which was first detected 70 years ago, came into play in recent years. In 1998, there was an exciting report in the journal Science by Kramer et al showing the antidepressant activity of an SP receptor antagonist. In the following, we will give a comprehensive overview of the nature of SP, the neuropeptide family it belongs to, and current data regarding the activity of SP receptor antagonists as psychotropic drugs.

**Substance P and the tachykinin family**

SP was the first known neuropeptide. Von Euler and Gaddum isolated SP from extracts of intestine and from brain as one of many substances. As it was in the powdered form, they named it substance P. In the first experiments, SP stimulated contractions of rabbit-ileum in an atropine-resistant manner. This first report on SP was published in 1931. In 1953, SP was recognized as a sensory neurotransmitter by Lembeck et al. It was more than 10 years later that SP was isolated from bovine

**Keywords:** antidepressant drug; anxiolytic drug; neuropeptide; NK1 receptor antagonist; substance P; tachykinin
hypothalamus and sequenced by Susan Leeman and colleagues, culminating in her efforts to identify a tissue component that stimulates salivation in rats. Another 10 years later, the other two mammalian tachykinins were discovered: the cationic peptide neurokinin A (NKA, formerly named substance K) and the anionic peptide neurokinin B (NKB). The tachykinins (tachys = swift) evoke a sharp contraction of the smooth muscle of the gut. These tachykinins are involved in multiple physiological processes, as demonstrated by their widespread distribution. In the periphery, they function as potential regulators of blood flow, vascular permeability, salivation, gastrointestinal motility, intestinal secretion, micturition, and leukocyte activity. Moreover, they act as pain transmitters from the periphery. In the central nervous system (CNS), tachykinins act as neurotransmitters and neuromodulators.

Tachykinin genes and synthesis

There are two genes encoding for the synthesis of the three tachykinins SP, NKA, and NKB: the prepro-tachykinin I (PPTI) gene encodes for SP and NKA, while the PPTII gene encodes for NKB. Through alternative splicing, the PPTI gene can express four different forms (α, β, γ, and δ) of mRNA. All of these forms are precursors of substance P, but only the β and γ forms also encode for the synthesis of NKA and its elongated forms neuropeptide K and neuropeptide γ. The mRNA generates the so-called grandfather peptide, the prepropeptide. The enzymatic cleavage to the “paternal” propeptide is done inside the endoplasmic reticulum. The last step in generating the active peptide is carried out by converting enzymes in cytoplasmic vesicles. Once the neuropeptides have been released, they are inactivated by catabolic peptidases. The tachykinins are degraded by multiple peptidases in the tissue including the angiotensin-converting enzyme (ACE). There is no reuptake mechanism, as known for the monoamine neurotransmitters.

Anatomic distribution of tachykinins within the CNS

SP is widely distributed throughout the CNS and the myenteric and submucous nerve plexuses of the gut. In the brain, SP is found in the midbrain periaqueductal gray, nucleus raphe magnus, and nucleus reticularis gigantocellularis pars α, which are important structures in the endogenous pain control system. Large numbers of SP-containing neurons have been found in the human posterior hypothalamus and basal forebrain, indicating an involvement of SP in hypothalamic functions such as sexual behavior or pituitary hormone release. SP is also found in the basal ganglia, nucleus accumbens, and—in lower levels—in the cerebral cortex. Moreover, there is evidence that SP interacts with dopaminergic neurons of nigrostriatal, limbic, and forebrain nuclei. NKB neurons are present in the anterior hypothalamus and the basal forebrain, indicating a complementary distribution from SP neurons. All three tachykinins are represented in the corpus striatum.

Colocalization of substance P with other neurotransmitters in the brain

In the human brain, 5-HT and SP coexist in a substantial proportion of the cell population of the dorsal raphe nucleus, the current target for antidepressant drug treatment. Almost 50% of the serotonergic neurons in the dorsal raphe nucleus, projecting to the forebrain, and 25% of the serotonergic neurons in the median raphe nucleus express SP mRNA. SP and 5-HT are colocalized in cat ventral medullary neurons and in serotonergic neuronal afferents to the hypoglossal nucleus of the rat. Moreover, SP is coexpressed with the serotonin receptor subtypes 5-HT2A, 5-HT2C, and 5-HT6 in rat striatum. It is remarkable that the expression of SP in the striatum, substantia nigra, and amygdala is reduced after chronic treatment with the antidepressant drugs imipramine, desipramine, clomipramine, amoxapine, and mianserin. Imipramine and desipramine also reduce the amount of SP in the hippocampus, while its reduction in the septum is only induced by mianserin.
The colocalization of SP and NE is demonstrated by the existence of SP-containing axon terminals in the locus ceruleus. Direct application of SP to the locus ceruleus has an excitatory effect via the neurokinin NK1 receptor. SP is also colocalized with dopaminergic neurons in the nucleus accumbens. SP is under the stimulatory control of dopaminergic neurons, projecting to the substantia nigra pars compacta and to the internal segment of the globus pallidus. Blockade of dopaminergic transmission by reserpine decreases the levels of SP mRNA, since it is under the stimulatory control of dopamine. Chronic treatment with amphetamine was found to be without effect on dopamine receptor levels in the striatum, but markedly increased the SP mRNA levels. Some studies suggest that the pain-suppression system involving the activation of mesolimbic dopaminergic neurons is naturally triggered by exposure to stress, through the endogenous release of opioids and SP in the midbrain. SP is also coexpressed with a wide variety of other neuropeptides and neurotransmitters, and even with neuronal nitric oxide synthase.

**Neurokinin receptors**

Three distinct neurokinin receptors are known: NK1, NK2, and NK3. SP is the most potent tachykinin for the NK1 receptor, whereas NKA exhibits the highest affinity for the NK2 receptor and NKB for the NK3 receptor. Recently, the NK4 receptor, which was initially claimed to be an atypical opioid receptor, was shown to respond potently to NKB in the rat, but its detection in human tissue has not been possible to date. However, it must be pointed out that all mammalian tachykinins have limited selectivity for a particular neurokinin receptor. This is due to the common C-terminal amino acid sequence, which is essential for the biological activity of the tachykinins. The neurokinin receptors are G-protein–coupled receptors with the characteristic seven-membrane-spanning domains. In general, several mechanisms prevent the uncontrolled stimulation of cells by neurotransmitters that interact with G-protein–coupled receptors: (i) removal of the agonist from the extracellular fluid by degradation or reuptake (the latter is not relevant to the tachykinins, as stated above); (ii) desensitization of the receptor by uncoupling from the G-proteins to minimize the signal transduction cascade; and (iii) endocytosis of the agonist-stimulated receptor, depleting the plasma membrane of high-affinity receptors. The NK1 receptor appears to be desensitized by phosphorylation, independently of receptor internalization, while resensitization requires endocytosis, recycling, and dephosphorylation. The prompt tachyphylaxis of the NK1 receptor after exposure to the agonist is, however, linked to the rapid receptor internalization.

**Anatomic distribution of neurokinin receptors within the CNS**

A wide variety of brain regions express the NK1 receptor. Notably, the raphe nuclei, locus ceruleus, striatum, the nucleus accumbens, the hippocampus, the lateral nucleus of the hypothalamus, the habenula, the interpeduncular nucleus, the nucleus of the tractus solitarius, and the substantia nigra are all rich in NK1 receptors. NK2 receptors are sparsely distributed in the CNS. They can be found in low amounts in various regions, such as the striatum. The third type of neurokinin receptor, the NK3 receptor, is strikingly prevalent in midcortical laminae throughout the cortex. The patterns of expression are therefore very different between the NK1, NK2, and NK3 receptors. NK4 receptor mRNA is widely expressed in neurons in the rat CNS, including cerebral cortex, hippocampus, and hypothalamus. The NK1 receptor is also coexpressed with nitric oxide synthase in striatal interneurons in the rat. In the spinal cord, NK1 receptors are localized on second-order sensory neurons, receiving nociceptive inputs. The NK1 receptor signal induces a slowly developing sustained depolarization, while the fast input to second-order sensory neurons is mediated by the excitatory amino acid glutamate through the N-methyl-D-aspartate (NMDA) receptor.

**Specific actions of the neurokinin receptors**

Elliott and Iversen described the diverse effects of SP after intracerebroventricular (ICV) administration or direct application into the ventral tegmental area of the mesencephalon of rat brain, which caused increased locomotor activity, grooming behavior, and wet dog
shakes. Repetitive hind paw tapping was also shown to result from activation of central NK1 receptors in gerbils. SP locally injected into the caudal pontine reticular nucleus dose-dependently increases the amplitude of the acoustic startle response in rats. Not only simple movements are induced by SP. Even complex behavior in animal models of anxiety and depression can be modulated by NK receptor activation. ICV infusion of the SP analogue, dimethyl-C7, was found to produce aversion in a place-conditioning paradigm. Moreover, ICV administration of SP, NKA, and NK1- and NK2-selective agonists produces an anxiogenic effect in the plus-maze test, the mouse model for anxiety behavior. In contrast, the synthetic NK3 agonist senktide has an anxiolytic effect. This again demonstrates the differential role of the three NK receptors. However, the complexity of the tachykinin system is also represented by differential effects within one NK receptor subtype, as the same receptor can exert contrary effects upon stimulation in different brain regions. One example is the anxiogenic effect of SP microinjection into the rat periaqueductal gray, whereas injection into the nucleus basalis produces an anxiolytic effect. Maternal separation of guinea-pig pups was shown to cause internalization of the NK1 receptors in the basolateral nucleus of the amygdala, suggesting the binding of SP to its receptor as a response to separation stress. In contrast, administration of the NK1 receptor agonist GR73632 induced pronounced long-lasting audible vocalizations, that could be attenuated by pretreatment with the antidepressant drug imipramine. To demonstrate the direct relationship between NK1 receptors and anxious behavior, the gene coding for the NK1 receptor was manipulated by deleting the first two transmembrane domains of the receptor molecule. This genetic disruption of the NK1 receptor markedly reduced anxiety-related behavior in the elevated plus-maze, novelty-suppressed feeding, and maternal separation paradigms. However, knock-out mice that totally lacked the NK1 receptor did not exert changed anxiety-related behavior in the open field test, but were markedly less aggressive than NK(+/+) mice in the resident intruder test of aggression. Consistent with these data, SP has been shown to evoke defensive rage in cats through an amygdalo-hypothalamic pathway. Systemic or intrahypothalamic infusion of the NK1 receptor antagonist CP96345 blocked this defensive rage in a similar manner to tricyclic antidepressants. Besides its role in modulating behavior, SP also exerts an important immunomodulating role within the CNS. Local administration of SP increases the interferon-γ (IFN-γ)-induced upregulation of antigen-presenting major histocompatibility complex (MHC) molecules in the brainstem, while administration of an NK1 receptor antagonist has the opposite effect. Moreover, SP has the potency to influence the so-called T helper 1/ T helper 2 (Th1/Th2) balance in the peripheral immune system, leading to the breakdown of the commitment to a particular T helper cell type. This is most interesting, as a predominance of the Th1-like, IFN-γ-related immune response was proposed in major depression. In summary, the immunomodulatory potency of SP may be a relevant component in the pathophysiology of major depression.

**Neurokinin receptor antagonists**

The first peptidergic NK1 receptor antagonists were synthesized in the early 1980s as useful tools for the investigation of the endogenous NK1 ligands. Ten years later, Snider and colleagues established the first non-peptide NK1 receptor antagonist. It was the first step in the race for a pharmacological compound to antagonize the SP signal. It was only 2 years later that the binding epitopes of SP and the new antagonist were detected: the tachykinin binds to the extracellular loops of the receptor, while the nonpeptide antagonists bind more deeply in the transmembrane segments of the receptor molecule. In the meantime, a great variety of nonpeptide antagonists for the NK1, NK2, and NK3 receptors have become available.

**Basic pharmacological studies on neurokinin receptor antagonists**

The important modulating and enhancing role of SP in nociception led to the idea of introducing NK1 receptor antagonists as antinociceptive drugs. A lot of effort was made toward the development of NK1 receptor antagonists for the treatment of pain. Although NK1 receptor antagonists appeared to act synergistically to inhibit NMDA receptors on second-order sensory neurons, they exhibited only weak potency in acute pain. However, antinociceptive efficacy could be observed in nociceptive models of chronic pain. This may be relevant to the treatment of the fibromyalgia syndrome (FM), a syn-
drome, characterized by chronic widespread pain and depression-like symptoms. Serum and cerebrospinal fluid (CSF) levels of SP are increased in FM, suggesting its probable role in the pathophysiology of FM.71 We were able to demonstrate a relationship between SP levels and intensity of pain perception in FM patients.72 Thus, the therapeutic use of NK1 receptor antagonists in FM may be a successful treatment strategy in FM, although they have failed to show antinociceptive efficacy in other chronic pain syndromes like peripheral neuropathy, osteoarthritis, or migraine.73

Since central administration of SP was shown to induce depression-like and anxious behavior (see above), the NK1 receptor antagonists were tested in several animal models of depression and anxiety. Vocalization evoked in guinea-pig pups or neonatal mice by transient maternal separation could be attenuated by systemic administration of several NK1 receptor antagonists, such as CP99994, L760735, or L733060.2,74 This effect was comparable to that of clinically used antidepressants (phenelzine, imipramine, fluoxetine) and anxiolytics (diazepam, buspirone). The dose-dependent antidepressant-like effect of another NK1 receptor antagonist, NKP608, was demonstrated in the chronic mild stress model of depression in rats, where the magnitude of the effect was similar to antidepressants in clinical use, but with a faster onset of action.75 The same NK1 receptor antagonist also exerted anxiolytic efficacy in rat social interaction tests.76 As shown by microinjection experiments of NK1 receptor antagonists, the amygdala appears to be one of the sites of action.77

More evidence for the antidepressant activity of NK1 receptor antagonists is given by their modulation of the serotonergic and norepinephrinergic systems. Systemic administration of an NK1 receptor antagonist enhances the firing rate of the locus ceruleus in response to stress.78 Recently, the activating effect of sustained NK1 receptor blockade on postsynaptic 5-HT1a autoreceptors was shown.79 The functional relationship between the NK1 receptor and the serotonergic system was also demonstrated by studies on NK1 knock-out mice. The constitutive lack of NK1 receptors appeared to be associated with a downregulation and functional desensitization of 5-HT1a autoreceptors. The serotonin receptor subtype 1a has been suggested to be critically involved in antidepressant action of selective serotonin-reuptake inhibitors (SSRIs) and its downregulation and desensitization in NK1 knock-out mice is equivalent to the effect of chronic treatment with SSRI antidepressants.79 Studies using NK1 receptor antagonists are not the only ones to show the anxiolytic and antidepressant potency of antagonizing the tachykinin receptors. The selective blockade of the NK2 receptor also exhibited the potency of antidepressant-like action. A recently published study demonstrated the positive effect of the NK2 receptor antagonist SR48968 on the mobility in the forced swimming test in mice and rats, and on the maternal separation–induced vocalizations in guinea-pig pups. This behavioral effect was associated with a reduced separation-induced increase in the number of neurons displaying NK1 receptor internalization in the amygdala.80 In contrast, the NK3 receptor seems to play a differential role in depression-like behavior: another recent study using the forced swimming test as mouse-model of depression showed the positive effect of the NK3 receptor agonist aminosenktide. Stimulation of the NK3 receptor shortened the time of immobility to the same extent as the prototypic antidepressant desipramine in two out of three investigated mouse lines.81 The anxiolytic effect of NK3 receptor agonists had already been shown by the elevated plus-maze test.82 These antidepressant-like and anxiolytic potentials of NK3 agonist properties may be related to the activation of the endogenous opioid system through NK3 receptor stimulation, as shown previously.83

**Clinical pharmacological studies on neurokinin receptor antagonists**

In 1998, Mark Kramer and colleagues published the first report of a clinical study testing the antidepressant efficacy of an NK1 receptor antagonist.84 This randomized, double-blind, placebo-controlled and active (paroxetine)-controlled study investigated the safety and efficacy of MK869, a selective NK1 receptor antagonist. This study has been subject of several more or less extensive reviews and commentaries,73,85-88 and so we will just give a short overview of the most important findings here. Outpatients with major depressive disorder and moderately high anxiety levels received a single daily dose of 300 mg MK869 (n=66), 20 mg paroxetine (n=68), or a placebo (n=64) for 6 weeks in four different study centers. Efficacy measurements were made at the end of weeks 1, 2, 4, and 6 by the Hamilton Depression scale total score (HAM-D21) and the Clinical Global Impressions Severity (CGI-S) scale. The principal outcome was
REFERENCES

1. Carlsson A. A paradigm shift in brain research. Science. 2001;294:1021-1024.
2. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science. 1998;281:1640-1645.
3. von Euler US, Gaddum JH. An unidentified depressor substance in cer- vical spinal cord. J Physiol Lond. 1953;219:197-213.
4. Lembbeck F. Zur Frage der zentralen Ubertragung afferenter Impulse III. Mitteilung. Das Vorkommen und die Bedeutung der Substanz P in den dor-salen Wurzeln des Rückenmarks. Naunyn Schmiedebergs Arch Pharmacol. 1953;219:197-213.
5. Chang MM, Leeman SE, Niall HD. Amino-acid sequence of substance P. Nat New Biol. 1971;232:86-87.
6. Mantyh PW, Maggio JE, Hunt SP. The autoradiographic distribution of kassinin and substance K binding sites is different from the distribution of substance P binding sites in rat brain. Eur J Pharmacol. 1984;102:361-364.
7. Kanazawa I, Ogawa T, Kimura S, Munekata E. Regional distribution of substance P immunoreactivity in the rat brain. Neurosci Lett. 1986;60:5-6.
8. Kanazawa I, Ogawa T, Kimura S, Munekata E. Regional distribution of substance K immunoreactivity in the rat brain. Neurosci Lett. 1986;60:5-6.
9. Strand FL. Neuropeptides: Regulators of Physiological Processes. 1st ed. Cam- bridge, Mass: The MIT Press; 1999.
10. Lang S, Spier G. Neurochemical characterization of preprotachykinin A(50-79) immunoreactivity in the rat. Regul Pept. 1995;57:183-192.
11. Krause JE, Chirgwin JM, Carter MS, Xu ZS, Hershey AD. Three rat preprotachykinin mRNAs encode the neuropeptides substance P and neurokinin A. Proc Natl Acad Sci U S A. 1987;84:881-885.
12. Fiskerstrand C, Quinn JP. The molecular biology of preprotachykinin-A gene expression. Neuropeptides. 1996;30:602-610.
13. Hokfelt T, Pernow B, Wahren J. Substance P: a pioneer amongst neu- ropeptides. J Intern Med. 2001;249:27-40.
14. Wang LH, Ahmad S, Benter IF, Chow A, Mizutani S, Ward PE. Differential processing of substance P and neurokinin A by plasma dipetidyl[(amino)peptidase IV, aminopeptidase M and angiotensin con- verting enzyme. Peptides. 1991;12:1357-1364.
15. Csuhai E, Little SS, Hersh LB. Inactivation of neuropeptides. Prog Brain Res. 1995;104:131-142.
16. Stahl SM. Peptides and psychiatry. Part 1. How synthesis of neuropep- tides differs from classical neurotransmitter synthesis. J Clin Psychiatry. 1999;60:5-6.
17. Li YQ, Wang ZM, Zheng XH, Shi JW. Central origins of substance P-like immunoreactive fibers and terminals in the spinal trigeminal caudal subnucleus in the rat. Brain Res. 1996;719:219-224.
El papel de la sustancia P en la depresión y implicaciones terapéuticas

La sustancia P (por “polvo”), identificada como una taquiquinina intestinal en 1931 e involucrada en el control de otras múltiples funciones autonómicas, especialmente en la transmisión del dolor, es el foco de una intensa investigación básica y en psiquiatría clínica como un neurotransmisor, neuromodulador e inmunomodulador central, junto a las neuroquininas hermanas A y B (NKA y NKB), descubiertas en 1984. La sustancia P se distribuye extensamente a través del sistema nervioso central, donde a menudo se co-localiza con serotonina, noradrenalina y dopamina. Se han sintetizado muchos agonistas y antagonistas de receptores de neuroquininas (NK) y algunos de ellos se han evaluado clínicamente. Un estudio doble ciego de MK869, un antagonista selectivo del receptor NK1 que bloquea la acción de la sustancia P demostró actividad significativa al compararlo contra el placebo y menos efectos sexuales colaterales que la paroxetina en pacientes ambulatorios con depresión mayor y ansiedad moderada. La sustancia P, que es degradada por la enzima convertidora de angiotensina (ECA), puede mediar la modulación de la evolución terapéutica de los trastornos afectivos a través del polimorfismo funcional dentro del gen de la ECA: el alelo D se asocia con niveles más elevados de ECA y un aumento en la degradación del neuropéptido. Esto se traduce en que pacientes con depresión mayor que poseen el alelo D tienen puntajes menores de depresión y hospitalizaciones más breves. La determinación genética del polimorfismo de la ECA podría así identificar a aquellos pacientes con depresión mayor que probablemente se beneficiarían con una terapia con antagonistas del receptor NK1.

Rôle de la substance P dans la dépression : implications thérapeutiques

La substance P (pour poudre), identifiée comme une tachykinine intestinale en 1931 et impliquée dans le contrôle de nombreuses autres fonctions autonomes, en particulier la transmission de la douleur, a suscité d’intenses recherches cliniques et fondamentales en psychiatrie en tant que neurotransmetteur, neuromodulateur et immunomodulateur central, parallèlement aux neurokinines œurs A et B (NKA, NKB), découvertes en 1984. La substance P est largement répandue dans le système nerveux central où elle coexiste souvent avec la sérotonine, la noradrénaline et la dopamine. De nombreux agonistes et antagonistes des récepteurs aux neurokinines (NK) ont été synthétisés et pour certains cliniquement testés. Une étude en double aveugle du MK869, un antagoniste sélectif du récepteur NK1 qui bloque l’action de la substance P, a montré une activité significative vs placebo et moins d’effets secondaires d’ordre sexuel que la paroxétine chez les patients ambulatoires souffrant d’une dépression sévère et d’une anxiété modérée. La substance P, qui est dégradée par l’inhibiteur de l’enzyme de conversion de l’angiotensine (IEC), pourrait médier la modulation de l’évolution thérapeutique des troubles affectifs par un polymorphisme fonctionnel au sein du gène de l’IEC : l’allèle D est associé à des concentrations plus élevées d’IEC et une augmentation de la dégradation des neuropeptides ; par conséquent les patients souffrant d’une dépression sévère et porteurs de l’allèle D présentent des scores de dépression plus faibles et des hospitalisations plus courtes. Le génotypage du polymorphisme des IEC pourrait ainsi permettre d’identifier les patients ayant une dépression sévère susceptibles de bénéficier au mieux d’un traitement par antagonistes des récepteurs aux NK1.
aspects on the distribution of 5-HT and its coexistence with substance P and TRH in cat ventral medullary neurons. J Chem Neuropathol. 1994;7:3-12.

25. Henry JN, Manaker S. Colocalization of substance P or enkephalin in serotoninergic neuronal afferents to the hypoglossal nucleus in the rat. J Comp Neurol. 1998;391:491-505.

26. Ward RP, Dorsa DM. Colocalization of serotonin receptor subtypes 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{3} with neuropeptides in rat striatum. J Comp Neurol. 1996;370:405-414.

27. Shirayama Y, Mitsuhashi H, Takehashi M, Ichikawa H, Takahashi K. Reduction of substance P after chronic antidepressants treatment in the striatum, substantia nigra and amygdala of the rat. Brain Res. 1996;739:70-78.

28. Hahn MK, Bannon MJ. Tachykinin NK1 receptor antagonists enhance stress-induced c-fos in rat locus coeruleus. Eur J Pharmacol. 1998;348:155-160.

29. Cheeseman HJ, Pinnock RD, Henderson G. Substance P excitation of rat locus coeruleus neurones. Eur J Pharmacol. 1983;94:93-99.

30. Guyenet PG, Aghajanian GK. Excitation of neurons in the nucleus locus coeruleus by substance P and related peptides. Brain Res. 1977;136:178-184.

31. McLean S, Ganon AH, Seeger TF, et al. Activity and distribution of binding sites in brain of a nonpeptide substance P (NK1) receptor antagonist. Science. 1991;251:437-439.

32. Pickel VM, Joh TH, Chan J. Substance P in the rat nucleus accumbens: ultrastructural localization in axon terminals and their relation to dopaminergic afferents. Brain Res. 1988;444:247-264.

33. Le Moine C, Normand E, Bloch B. Phenotypical characterization of the rat striatal neurons expressing the D_{1} dopamine receptor gene. Proc Natl Acad Sci U S A. 1991;88:4205-4209.

34. Jaber M, Normand E, Bloch B. Effect of reserpine treatment on enkephalin mRNA in the rat striatum: an in situ hybridization study. Brain Res Mol Brain Res. 1995;32:156-160.

35. Atter J, Stewart J. The role of dopamine in the nucleus accumbens in alcohol. Life Sci. 1998;63:2269-2287.

36. Dufourny L, Warenbourg M, Jolivet A. Quantitative studies of prepro-terone receptor and nitric oxide synthase colocalization with somatostatin, or neurotensin, or substance P in neurons of the guinea pig ventrolateral hypothalamic nucleus: an immunocytochemical triple-label analysis. J Chem Neuropathol. 1999;17:33-43.

37. Saria A. The tachykinin NK1 receptor in the brain: pharmacology and putative functions. Eur J Pharmacol. 1993;375:51-60.

38. Donaldson LF, Haskell CA, Hanley MR. Messenger RNA localization and further characterisation of the putative tachykinin receptor NK4 (NK3B). Receptors Channels. 2001;7:259-272.

39. Li J, Kaneko T, Mizuno N. Colocalization of neuronal nitric oxide synthase and neurokinin-1 receptor in striatal interneurons in the rat. Neurosci Lett. 2001;310:109-112.

40. Elliott PJ, Iversen SD. Behavioural effects of tachykinins and related peptides. Brain Res. 1986;381:68-76.

41. Bristow LJ, Young L. Chromodacryorrhea and repetitive hind paw tapping: models of peripheral and central tachykinin NK1 receptor activation in gerbils. Eur J Pharmacol. 1994;253:245-252.

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

43. Elliott PJ. Place aversion induced by the substance P analogue, dimethyl-c7, is not state dependent: implication of substance P in aversion. Exp Brain Res. 1988;73:354-356.

44. Teixeira RM, Santos AR, Ribeiro SJ, Calixto JB, Raa GE, De Lima TC. Effects of central administration of tachykinin receptor agonists and antagonists on plus-maze behavior in mice. Eur J Pharmacol. 1996;311:7-14.

45. Ribeiro SJ, Teixeira RM, Calixto JB, De Lima TC. Tachykinin NK(3) receptor involvement in anxiety. Neuropeptides. 1999;33:181-188.

46. Aguas MS, Brandao ML. Effects of microinjections of the neuropeptide substance P in the dorsal periaqueductal gray on the behaviour of rats in the plus-maze test. Physiol Behav. 1996;60:1183-1186.

47. Hanenohrl RU, Jentjens O, Souza Silva MA, Tomaz C, Huston JP. Anxiety-like-like action of neurokinin 1 substance P administered systemically or into the nucleus basalis magnocellularis region. Eur J Pharmacol. 1998;354:123-133.

48. Santarelli L, Gobbi G, Debs PC, et al. Genetic and pharmacological disruption of neurokinin 1 receptor function decreases anxiety-related behaviors and increases serotonin function. Proc Natl Acad Sci U S A. 2001;98:1912-1917.

49. de Felice C, Herrera JF, O’Brien JA, et al. Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. Nature. 1998;392:394-397.

50. Siegel A, Schubert KL, Shaikh MB. Neurotransmitters regulating defensive rage behavior in the cat. Neurosci Biobehav Rev. 1997;21:733-742.

51. Saikia MB, Steinberg A, Siegel A. Evidence that substance P is utilized in medial amygdaloid facilitation of defensive rage behavior in the cat. Brain Res. 1993;625:283-294.

52. Dubinsky B, Goldberg ME. The effect of imipramine and selected drugs on c-fos expression elicited by hypothalamic stimulation in the cat. Neuropharmacology. 1971;10:537-545.

53. McCluskey LP, Lampson LA. Local immune regulation in the central nervous system by substance P vs glutamate. J Neuroimmunol. 2001;116:136-146.

54. Levine M. Neuropeptides, by direct interaction with T cells, induce cytokine secretion and break the commitment to a distinct T helper phenotype. Proc Natl Acad Sci U S A. 1998;95:12544-12549.

55. Schwarz MJ, Chiang S, Müller N, Ackenheil M. T-helper-1 and T-helper-2 responses in psychiatric disorders. Brain Behav Immun. 2001;15:340-370.

56. Folkers K, Horig J, Rosel S, Bjorkroth U. Chemical design of antagonists of substance P. Acta Physiol Scand. 1981;111:505-506.

57. Snider RM, Constantine JW, Lowe JA, III, et al. A potent nonpeptide antagonist of the substance P (NK1) receptor. Science. 1991;251:435-437.

58. Gether U, Johansen TE, Snider RM, Lowe JA III, Nakanishi S, Schwartz TW. Different binding epitopes on the NK1 receptor for substance P and nonpeptide antagonist. Nature. 1993;362:345-348.

59. Radhakrishnan V, Iyengar S, Henry JN. 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. 1998;83:1251-1260.

60. Russell L. Neurochemical pathogenesis of fibromyalgia syndrome. J Musculoskeletal Pain. 1996;4:61-92.

61. Schwarz MJ, Spaat M, Müller-Bardorff H, Pongratz D, Bondy B, Ackenheil M. Relationship of substance P, 5-hydroxyindoleacetic acid and tryptophan in serum of fibromyalgia patients. J Neuroimmunol. 2001;111:505-506.

62. Rupniak NM, Kramer MS. Discovery of the antidepresant and anti-epileptic efficacy of substance P receptor (NK1) antagonists. Trends Pharmacol Sci. 1999;20:485-490.

63. Rupniak NM, Carlson EC, Harrison T, et al. Pharmacological blockade or genetic deletion of substance P (NK1) receptors attenuates neonatal vocal-
Substance P antagonists as antidepressants - Schwarz and Ackenheil

Dialogues in Clinical Neuroscience - Vol 4 · No. 1 · 2002

isation in guinea-pigs and mice. Neuropharmacology. 2000;39:1413-1421.
75. Papp M, Vassout A, Gentsch C. The NK1-receptor antagonist NK608 has an antidepressant-like effect in the chronic mild stress model of depression in rats. Behav Brain Res. 2000;115:19-23.
76. File SE. NK608, an NK1 receptor antagonist, has an anxiolytic action in the social interaction test in rats. Psychopharmacology (Berl). 2000;152:105-109.
77. Boyce S, Smith D, Carlson E, et al. Intra-amygdala injection of the substance P [NK(1) receptor] antagonist L-760735 inhibits neonatal vocalisations in guinea-pigs. Neuropharmacology. 2001;41:130-137.
78. Haddjeri N, Blier P. Sustained blockade of neurokinin-1 receptors enhances serotonin neurotransmission. Biol Psychiatry. 2001;50:191-199.
79. Froger N, Gardier AM, Moratalla R, et al. 5-Hydroxytryptamine (5-HT)\textsubscript{1A} autoreceptor adaptive changes in substance P (neurokinin 1) receptor knock-out mice mimic antidepressant-induced desensitization. J Neurosci. 2001;21:8188-8197.
80. Steinberg R, Alonso R, Griebel G, et al. Selective blockade of neurokinin-2 receptors produces antidepressant-like effects associated with reduced corticotropin-releasing factor function. J Pharmacol Exp Ther. 2001;299:449-458.
81. Panocka I, Massi M, Lapi O, Swiderski T, Kowalczyk M, Sadowski B. Antidepressant-type effect of the NK3 tachykinin receptor agonist aminosenkstic acid in mouse lines differing in endogenous opioid system activity. Peptides. 2001;22:1037-1042.
82. Ribeiro SJ, De Lima TC. Naloxone-induced changes in tachykinin NK3 receptor modulation of experimental anxiety in mice. Neurosci Lett. 1998;258:155-158.
83. Nutt D. Substance-P antagonists: a new treatment for depression? Lancet. 1998;352:1644-1646.
84. Argyropoulos SV, Nutt DJ. Substance P antagonists: novel agents in the treatment of depression. Expert Opin Investig Drugs. 2000;9:1871-1875.
85. Stout SC, Owens MJ, Nemiroff CB. Neurokinin(1) receptor antagonists as potential antidepressants. Annu Rev Pharmacol Toxicol. 2001;41:877-906.
86. Kramer MS. Update on Substance P (NK-1 receptor) antagonists in clinical trials for depression. Neuropeptides. 2000;34:255.
87. Kramer MS, Ball WA, Reines SA. Replication of the efficacy and tolerability of substance P antagonists in patients with major depression. American College of Neuropsychopharmacology (ACNP) 40th Anniversary Scientific Abstract Book. 2001. Abstract 128.
88. Baghai T, Schüle C, Zwanzger P, et al. Possible influence of the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene on therapeutic outcome in affective disorders. Mol Psychiatry. 2001;6:258-259.
89. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest. 1990;86:1343-1346.
90. Rigat B, Hubert C, Corvol P, Soubrier F. PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP1) (dipeptidyl carboxypeptidase 1). Nucleic Acids Res. 1992;20:1433.
91. Murphey LJ, Gainer JV, Vaughan DE, Brown NJ. Angiotensin-converting enzyme insertion/deletion polymorphism modulates the human in vivo metabolism of bradycardin. Circulation. 2000;102:829-832.