Tachykinin Receptors as Therapeutic Targets in Stress-Related Disorders

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Abstract: The first report demonstrating the therapeutic efficacy of an orally applied neurokinin-1 (NK1) receptor antagonist in depression was published 10 years ago. Although there were difficulties to reproduce this particular finding, a huge amount of data has been published since this time, supporting the potential therapeutic value of various tachykinin ligands as promising novel tools for the management of stress-related disorders including anxiety disorders, schizophrenia and depression. The present review summarizes evidence derived from anatomical, neurochemical, pharmacological and behavioral studies demonstrating the localization of tachykinin neuropeptides including substance P (SP), neurokinin A, neurokinin B and their receptors (NK1, NK2, NK3) in brain areas known to be implicated in stress-mechanisms, mood/anxiety regulation and emotion-processing; their role as neurotransmitters and/or neuromodulators within these structures and their interactions with other neurotransmitter systems including dopamine, noradrenaline and serotonin (5-hydroxytryptamine, 5-HT). Finally, there is clear functional evidence from animal and human studies that interference with tachykinin transmission can modulate emotional behavior. Based on these findings and on evidence of upregulated tachykinin transmission in individuals suffering from stress-related disorders, several diverse tachykinin receptor antagonists, as well as compounds with combined antagonist profile have been developed and are currently under clinical investigation revealing evidence for anxiolytic, antidepressant and antipsychotic efficacy, seemingly characterized by a low side effect profile. However, substantial work remains to be done to clarify the precise mechanism of action of these compounds, as well as the potential of combining them with established and experimental therapies in order to boost efficacy.

Key Words: Substance P, NKA, NKB, neurokinin, tachykinin, NK1 receptor, NK2 receptor, NK3 receptor, depression, anxiety, panic, schizophrenia, antidepressant, anxiolytic, stress, multi target approach.

1. INTRODUCTION

Mammalian tachykinins (neurokinins) including the three main members substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) are a group of neuropeptides which share a common carboxy-terminal amino acid sequence, Phe-X-Gly-Leu-Met-NH2, where X is a hydrophobic residue that is either an aromatic or a beta-branched aliphate [1, 2]. The three peptides are almost exclusively expressed in neurons and act as neurotransmitters and/or neuromodulators in the central nervous system [3]. More recently, a novel peptide was discovered which was termed hemokinin 1 because it was detected primarily in hematopoietic cells [2]. However, although this tachykinin has also been detected in the central nervous system, at least in the mouse brain [4], its neurotransmitter/neuromodulator function is not established so far. In contrast, other tachykinin-like peptides such as endokinins are localized and exert their effects mainly in the periphery [5, 6].

The tachykinins are encoded on three different genes, termed TAC1 (formerly preprotachykinin A, PPT-A), TAC3 (formerly PPT-B) and TAC4 (formerly PPT-C). SP and NKA are encoded by TAC1 [7], which produces four splice variants of exon 6: α- and δ-TAC1 yielding SP alone and β- and γ-TAC1 producing SP along with NKA [8-11]. Interestingly, species-dependent differential expression of TAC1 splice variants has been observed. For example, in the rat ß and γ-TAC1 mRNA are most abundant [12] suggesting that in many cases SP and NKA are synthesized together and released as co-transmitters. In contrast, NKB and HK-1/endokinins are generated from separate genes, TAC3 and TAC4, respectively [13-15].

1.1. Distribution of Tachykinins in the Central Nervous System

Most studies on the central distribution of the tachykinins have been carried out in the rat brain and have primarily focused on SP. By using immunohistochemical and in-situ hybridisation methods a widespread distribution of SP has been found in the mammalian brain. In various species, high levels of SP-immunoreactive cell bodies, fibres and terminals have been identified in many forebrain, midbrain and brainstem areas implicated in the modulation of stress, anxiety and mood responses such as the cingulate cortex, caudate putamen, nucleus accumbens, septum, hippocampus, amygdala, various hypothalamic areas as well as periaqueductal gray, dorsal raphe nucleus, locus coeruleus, various parabrachial nuclei and in the nucleus of the tractus solitarius [16-19]. Specifically, the extensive distribution of SP in limbic brain structures such as amygdala, septum and bed nucleus of the stria terminalis [16, 17, 20, 21] led to the conclusion

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that the SP system may play an important role in emotional and affective functions. In these regions, SP frequently coexists in the same neuron with other neuropeptides including neurokinins and with 'classical' neurotransmitters such as dopamine (DA), acetylcholine, serotonin (5-hydroxytryptamine, 5-HT), noradrenaline (NA), glutamate or GABA suggesting an important role as co-transmitter [22-24] (see chapter 1.5). In respect to affective disorders such as depression and anxiety disorders the colocalization with brain serotonergic and noradrenergic systems are of high relevance because these monominergic systems are known to be involved in the regulation of emotions including mood. Studies on the distribution of SP in the human brain have shown considerable similarity to that in the rat brain with particular dense distributions of immunoreactive fibres or neurons containing SP in cortical and hypothalamic areas, in the hippocampus, substantia nigra and brain stem areas [25-29]. However, despite this similarity there are also some species differences. For example, SP seems to be more abundant in human cortical and hippocampal areas compared to the rat brain [30, 31] indicating an increased SP involvement in higher brain functions with increasing phylogenetic complexity. Also in respect to colocalisation with other neurotransmitter systems species differences were found. For example, lower level of colocalisation of SP and 5-HT were detected in the dorsal raphe nucleus of rats compared to that of humans and monkeys [32-34]. However, the physiological significance of such species differences are not well documented.

Compared to SP, the other tachykinins have generally been found in lower concentrations in the central nervous system. As expected, NKA is highly co-localized with SP due to its derivation from the same precursor gene (see introduction). However, tissue measurements suggest that the ratio between these tachykinins can vary throughout several brain regions. For instance, in the striatum or substantia nigra the SP concentration is several times higher than that of NKA while in other areas such as hippocampus this ratio seems to be more balanced [35]. Nevertheless, it should be noted that using different antisera or extracts of distinct brain punches (e.g. subregions of a brain area) may provide different results as for example, even higher NKA concentrations (relative to SP) have been found in several regions such as frontal cortex, hippocampus and nucleus accumbens [36, 37]. Based on considerable variances between such studies and methodological limitations concerning tissue measurements quantitative comparisons should be interpreted with caution.

The distrubution of NKB, generated from TAC3 mRNA is different to that of SP and NKA. Neurons containing NKB immunoreactivity and precursor mRNA are present in the olfactory bulb and tubercle, some cortical regions, nucleus accumbens, hippocampus, septum, bed nucleus of stria terminalis, several hypothalamic regions, amygdala, medial habenula, periaqueductal gray, superior and inferior colliculus, substantia nigra and nucleus of the spinal trigeminal tract [38-41]. Although the distribution of NKB does overlap with that of SP, there are also some striking differences. For example, in the nigro-striatal system or in the raphe nuclei numerous SP labelled cells were found, while NKB labelling was very low [40]. On the other hand, in the hippocampus where only moderate amounts of SP were found at least in rats [42] the concentration of NKB seems to be very high [39]. Moreover, there are also examples for a distinct and complementary distribution pattern of SP and NKB neurons within a particular brain region such as the human hypothalamus where NKB was primarily found in the rostral hypothalamus, whereas SP predominated in the posterior hypothalamus [25]. Notably, there is also some evidence for a species difference in the NKB expression. In a very recent study it was shown that NKB and NK3 receptor expression in mice and rats are in part divergent [43]. For example, in the hippocampus of rats NKB has been found in the granular layer of the dentate gyrus, while in mice no such expression was found although NK3 receptor expression in this area was congruent in mice and rats [43]. These results might have implications for the interpretation of behavioral results concerning the NKB/NK3 receptor system in these species (see section 2.1.2).

1.2. Tachykinin Binding Sites: Classification and Characteristics

The biological effects of tachykinins are mediated through a family of seven transmembrane domain G-protein coupled receptors. The interaction of the tachykinins with their preferred receptor results in an elevation of intracellular Ca^{2+} via a phospholipase C, inositol trisphosphat and diacylglycerol signalling cascade [44]. In addition, the stimulation of adenylate cyclase and the increase of cyclic adenosine monophosphate has been reported after tachykinin receptor activation [45]. So far, three types of neurokinin receptors have been identified in mammals, neurokinin-1 (NK1), neurokinin-2 (NK2) and neurokinin-3 (NK3) receptors [46, 47]. The NK1 and NK3 binding sites are widely distributed in the mammalian brain whereas NK2 receptors are observed only in a few particular areas (see section 1.3, Fig. (**1**)). Although all endogenous neurokinins possess limited selectivity and, thus, can interact with all three receptor types, SP exhibits high affinity to the NK1 receptor, whereas NKA and NKB preferentially bind to the NK2 and NK3 receptors, respectively [2, 46-48]. This cross-talk among the three receptor types may, indeed, be of importance in pathophysiological states when tachykinin levels are thought to be exaggerated rather than during physiological conditions. A further complication is the proposal of different binding sites on the NK1 receptor, including the "classic" NK1 receptor binding site with high affinity for SP and low affinity to NKA and NKB, the "septide-sensitive" NK1 receptor site [49] where in addition to SP also NKA, NKB and some SP fragments (e.g. SP 6-11) bind with high affinity and finally a "new NK1-sensitive binding site" [5]. Species-dependent variation of the amino acid sequence of the NK1 receptor protein [50, 51] underlying different receptor pharmacology [52] has been noted. Although these variations do not affect the affinity of endogenous SP, however, they determine the species-related differences in the potency of non-peptide antagonists [50, 51], which is thought to be due to different binding epitopes on the NK1 receptor for SP and antagonists [53].

1.3. Distribution of Tachykinin Receptors in the Central Nervous System

The regional distribution of tachykinin receptors in the central nervous system has been studied in several species.

Autoradiographic and immunohistochemical studies have shown a widespread distribution of tachykinin receptors throughout the mammalian brain and have identified NK1 and NK3 receptor binding sites in higher densities than NK2 receptor sites [46]. While NK1 and NK3 receptors are widely distributed in the whole brain, NK2 receptors are only found in few structures including several cortical areas, hippocampus, nucleus accumbens, parts of the thalamus and lateral septum [16, 54]. The presence of NK2 receptor binding sites in several limbic structures is consistent with a possible role of this receptor type in the modulation of emotional processes (Fig. (**1**)). Similarly, also NK1 and NK3 receptors have been identified in brain areas involved in the control of anxiety and stress responses such as the prefrontal cortex, hippocampus, caudate putamen, septum, amygdala and various thalamic and hypothalamic nuclei, as well as periaqueductal gray, habenula, dorsal raphe and locus coeruleus [16, 17, 54-56] (Fig. (**1**)). Despite considerable overlap in some of these areas there are marked differences in distribution patterns, in particular, in specific subregions between these receptor types. For example, in the amygdala a strong NK1 receptor expression is found in the medial and cortical part extending into the basomedial part while NK3 receptors are present mainly deep in the basomedial and basolateral part [16, 54]. Similarly, in the septum NK1 receptors are abundant in both its lateral and medial parts [57] whereas NK3 receptors are almost exclusively expressed in its medial part [55]. Nevertheless, the greatest differences in NK1 and NK3 receptor distribution are evident in hypothalamic regions where NK3 receptors are more prominent than NK1 receptors [54] and (prefrontal) cortical regions where NK3 receptors are present in superficial and deep layers and NK1 receptors are more restricted to the upper cortical layers [58, 59]. Besides, there is also some evidence for interspecies differences in the expression of tachykinin receptors, in particular, in the hippocampus and cortex suggesting that these receptors mediate different functions in different species [58, 60, 61]. For instance, in cortical areas of the human but not rat brain NK3 receptors are found in high density on astrocytes [58, 59]. In contrast, in rats tachykinin receptors are expressed on glia cells in the brain of newborn animals only whereas in older animals these receptors are localised exclusively on neurons [62].

Although in most of these areas there is good accordance between the distribution of tachykinin peptide containing fibers and respective binding sites, an interesting aspect is an apparent mismatch between receptors and endogenous ligands in some areas. Most notably is the substantia nigra, where the concentration of SP is extremely high, but the expression of NK1 receptors is very low [17, 19]. A partially reversed situation seems to exist in the dorsal hippocampus with low SP levels and high densities of NK1 receptor binding sites [16]. Reasons for such mismatches may be (i) technical factors, (ii) the existence of yet undiscovered subtypes of neurokinin receptors [63] and (iii) their neuromodulatory character, i.e. that tachykinins can diffuse over long distances to bind to their receptors (volume transmission) [64, 65] making a direct relationship between the density of ligand innervation and the density of post-synaptic NK receptors not obligatory. Finally, since tachykinins can bind at

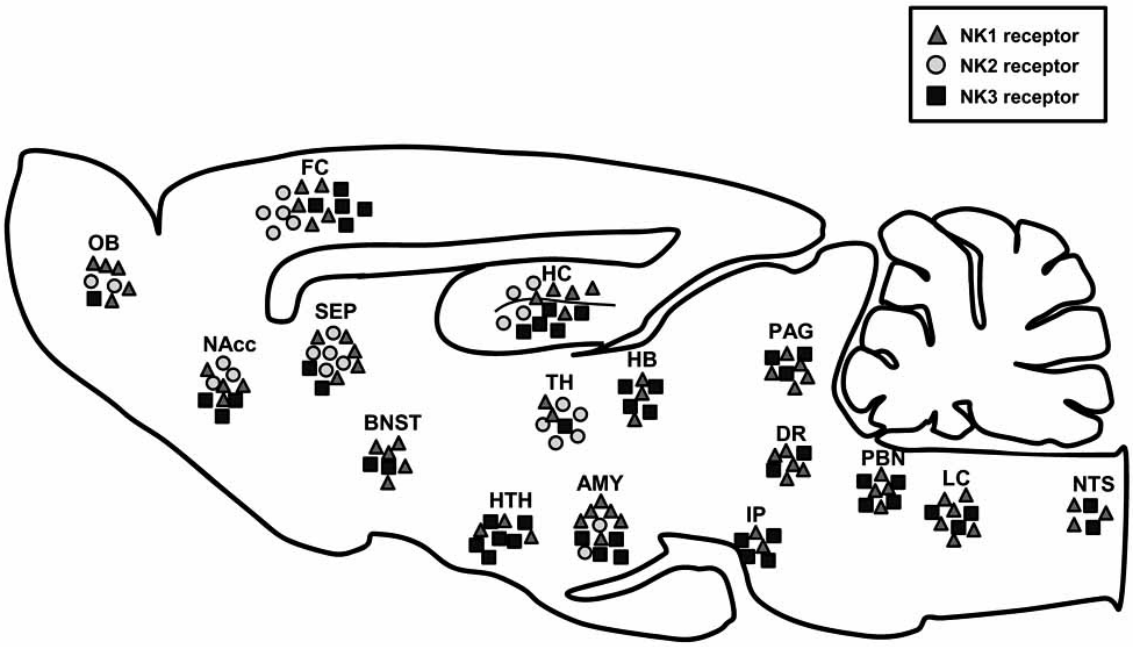

Fig. (1). Schematic drawing demonstrating the distribution and relative density of NK1, NK2 and NK3 receptors in rodent brain areas associated with emotional processing. Abbreviations: AMY, amygdala; BNST, bed nucleus of the stria terminalis; DR, dorsal raphe; FC/PFC, frontal/prefrontal cortex; HB, habenula; HC, hippocampus; HTH, hypothalamus; IP, interpedincular nucleus; LC, locus coeruleus; NAcc, nucleus accumbens; NTS, nucleus tractus solitarius; OB, olfactory bulb; PAG, periaqueductal gray; PBN, parabrachial nucleus; SEP, septum; TH, thalamus. Data from references [16, 17, 54, 55].

all three receptors, it may be speculated that under specific conditions (e.g. in stressed or pathophysiologically altered systems) the concentrations of distinct tachykinin peptides are high enough to activate other than the preferred tachykinin receptors.

1.4. Autoregulation of Tachykinin Transmission

Although data are limited and mainly concern the somatosensory system, the existence of a NK1 autoreceptor has been suggested [66], opening one direct possibility of a presynaptic automodulation of SP transmission. Both inhibitory and stimulatory actions of putative NK1 autoreceptors have been proposed. In the spinal cord it has been shown that the NK1 receptor antagonists RP67580 and SR140333 increase electrically evoked *in vitro* SP release from slices [67], which was taken as evidence for the existence of an inhibitory NK1 autoreceptor, since NK1 receptors are not present on inhibitory neurons such as GABAergic neurons in the investigated part of the spinal cord [66]. Unfortunately, data on possible autoregulation in supraspinal, in particular limbic areas are scarce. In our recent work we were able to provide some evidence for such an autoregulatory mechanism in the amygdala of the rat. By infusing a selective NK1 receptor antagonist locally into the medial amygdala, SP release is increased in this brain area suggesting a self-regulatory capacity of SP-mediated neurotransmission [68]. Although some anatomical evidence for a presynaptic localization of NK1 receptors on SP-containing terminals has been gained in distinct brain areas such as nucleus accumbens, periaqueductal gray and striatum [69-72], we could not detect a presynaptic localization of NK1 receptors on SP-containing terminals in the medial amygdala [68]. Hence, the observed inhibitory feedback regulation of SP release in this area most likely involves interaction with inhibitory neurons and neurotransmitter systems (e.g. GABAergic; see section 1.5). Interestingly, this inhibitory autoregulation of SP via NK1 receptors was not evident during an applied stressor disproving the idea that it may serve as a safety response aimed at preventing overstimulation. In contrast, it seems that in the medial amygdala the activation of NK1 receptors is further faciliated by endogenous SP in response to a stressful experience since NK1 receptor blockade stereoselectively reduced stress-induced SP release [68]. Thus, this self-regulatory capacity of SP-mediated neurotransmission differs under basal and stimulated/stressful conditions. Although the exact mechanisms underlying this effect are yet poorly understood, the further facilitation of stress-induced SP release may have important functional consequences via involvement of other tachykinin receptors in addition to NK1 such as NK2 and NK3 receptors which are also thought to play a role in the modulation of depression- and anxiety-like behavior (see section 2.1.2). Further studies should clarify the physiological and behavioural role of these receptors and their interaction in the amygdala during stressful situations.

1.5. Interaction of Tachykinins with Other Neurotransmitter Systems

Interaction with Amino Acids

Similar to most other neuropeptides, tachykinins widely coexist with classical neurotransmitters (see section 1.1). Moreover, it is well documented that intracerebral administration of tachykinins or adequate agonists can modulate the release of a number of neurotransmitters including acetylcholine, monoamines and amino acids indicating potential interaction of tachykinins with these neurotransmitter systems. In the cortex, for example, NK1 receptor activation promotes the release of GABA at synapses of principal neurons pointing towards a possible inhibitory role onto pyramidal output neurons [73]. This inhibitory effect on principal neurons does not seem to be mediated by a direct, but likely through an indirect effect via activation of inhibitory interneurons. Indeed, a dense expression of NK1 receptors on GABAergic interneurons within cortical areas is reported [74]. On the other hand, NK1 receptor activation has also been shown to excite cortical neurons possibly via activation of glutamate-containing interneurons resulting in an increased glutamate release [75]. Similar excitatory effects were found after NK3 receptor activation in the prefrontal cortex of guinea pigs [76] and cingulate cortex of gerbils [77]. In other forebrain areas such as hippocampus and amygdala tachykinins may regulate the synaptic input to principal neurons by increasing the excitability of GABAergic interneurons [78-80]. For example, in the basolateral amygdala of rats and guinea pigs NK1 receptors are largely restricted to GABA containing interneurons [79, 81] and NK1 receptor activation has shown to stimulate inhibitory synaptic transmission *in vitro* [79]. Similar to the NK1 receptor, the other two tachykinin receptors have been reported to modulate GABAergic transmission in various brain areas. For example, depending on the brain area activation of NK3 receptors can reduce [82] or enhance GABA release [83].

Interaction with Serotonin

There is also evidence for functional interaction between tachykinins and monoaminergic systems including the 5-HT and NA system which both are known to be implicated in the pathophysiology and treatment of mood disorders [84, 85]. First evidence for such a functional interaction comes from anatomical studies demonstrating high density of tachykinin receptors (e.g. primarily NK1 receptors) in monoaminergic nuclei such as dorsal raphe nucleus and locus coeruleus (see section 1.3). However, although NK1 receptors have been identified on serotonergic and noradrenergic cells suggesting a direct influence on the firing activity of monoaminergic neurons, the exact mechanisms by which tachykinins influence 5-HT and NA neurons are not completely understood. For instance, in the dorsal raphe nucleus several mechanisms have been proposed through which NK1 receptors affect the firing rate of 5-HT neurons (see section 3.1.1). Electrophysiological studies have shown that NK1 receptor blockade, either by antagonist treatment or by genetic disruption, increases the firing of dorsal raphe neurons and therefore results in enhanced serotonergic neurotransmission [86]. Based on these findings it has been proposed that the antidepressant effects of NK1 receptor antagonists may result from an increased central 5-HT transmission similar to that of established antidepressants such as selective serotonin reuptake inhibitors (SSRIs). However, despite these similarities, clear differences exist between mechanisms of action of SSRIs and NK1 receptor antagonists. For instance, SSRIs require prolonged administration for a significant clinical improvement. This delay is thought to be caused by compensatory changes resulting in a desensitization of somatodendritic 5-

HT_{1A} autoreceptors in the dorsal raphe nucleus following chronic SSRI administration and a delayed increase in 5-HT release in dorsal raphe projection fields [87]. In contrast, NK1 receptor antagonists may have a faster onset of 5-HT related therapeutic effects, because they exert their effects not exclusively by an attenuation of somatodendritic $5\text{-}HT_{1A}$ autoreceptor responsiveness [88], opening the possibility of faster increases in 5-HT release (see section 3.1.1). Indeed, we found increased 5-HT release in the lateral septum, an important dorsal raphe terminal region involved in emotional processing [89] after acute intraseptal NK1 receptor blockade [57]. Specifically, administration of the selective NK1 receptor antagonist L822429 locally into the lateral septum reversed the stress-induced decrease of extracellular septal 5-HT efflux coinciding with a reduction of depression-like behavior (Fig. (**2**)). Interestingly, we found similar effects also after a single systemic administration [57]. Thus, our data suggest that NK1 receptor antagonists can elicit an immediate, functionally significant facilitatory effect on 5-HT transmission locally in a terminal region of 5-HT neurons without a direct involvement of the interaction with neuronal firing at the cell body level of raphe neurons.

Interaction with Noradrenaline

In addition to alterations in 5-HT neuronal function, there is also evidence that tachykinins modulate the firing characteristics of ascending NA neurones originating in the locus coeruleus. These neurones are innervated by tachykinin-containing fibres and tachykinin receptors, mainly NK1 and NK3 receptors, are highly expressed in this brain area (see

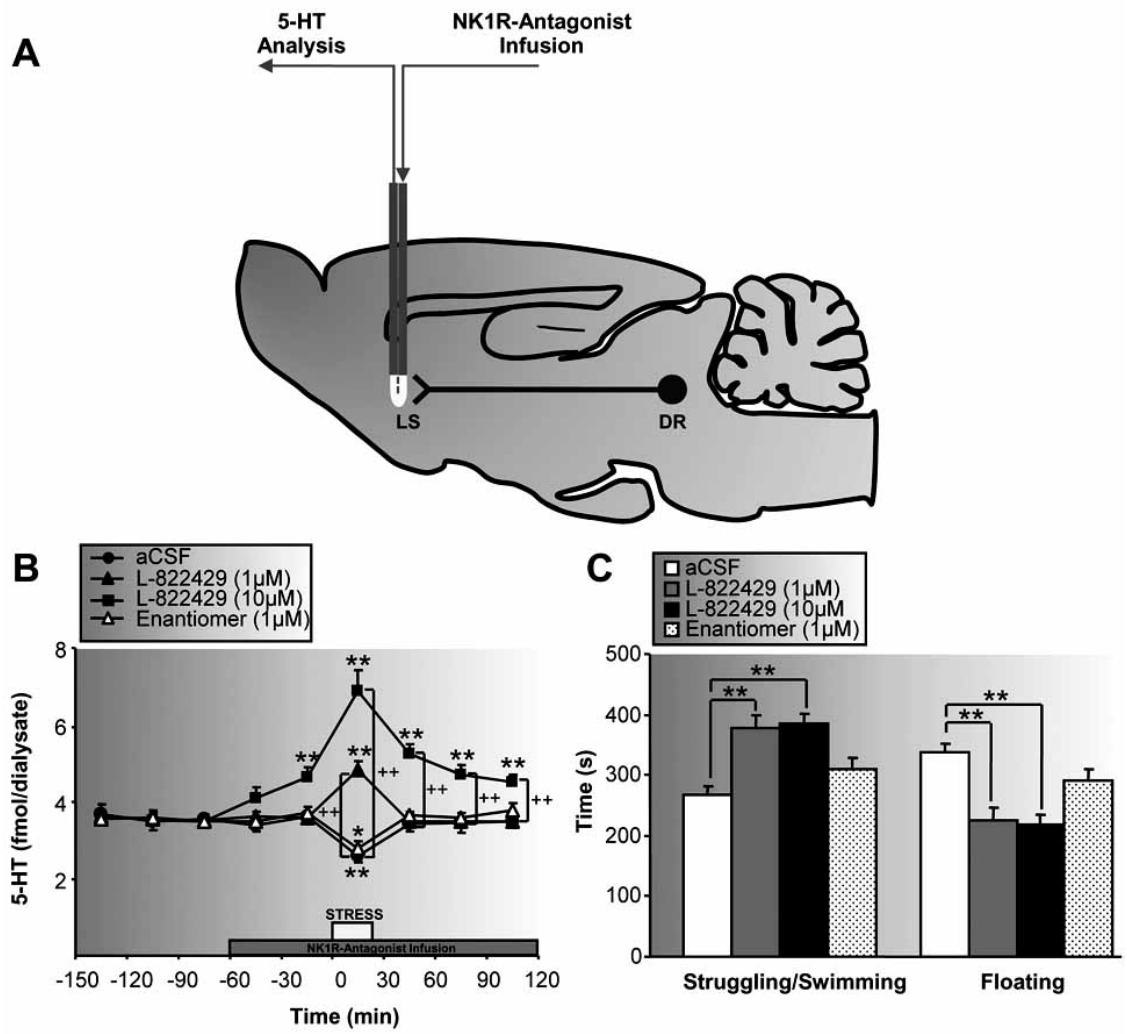

Fig. (2). Effects of NK1 receptor antagonism within the lateral septum on 5-HT release and stress-coping behavior of rats during forced swimming. (**A**) Schematic representation of the experimental set-up of the microdialysis study demonstrating the infusion of the NK1 receptor antagonist L822429 locally into the lateral septum (prominent terminal area of serotonergic dorsal raphe neurons) with concomitant measurements of extracellular 5-HT levels. (**B**) Intraseptal NK1 receptor blockade reverses the stress-induced decrease of extracellular 5-HT levels in the lateral septum. (**C**) Improved stress coping after intraseptal application of L822429. Note the effects of L822429 are selectively mediated by NK1 receptors since its less active enantiomer had no effect. Adapted, with permission, from reference [57].

section 1.3). Moreover, it is well documented that NK1 and NK3 receptor ligands modulate the firing rate of locus coeruleus neurons [90-95]. Microdialysis studies in freely moving animals have shown that NK1 receptor antagonists increase NA release in terminal fields of the locus coeruleus such as prefrontal cortex and hippocampus [95, 96]. Interestingly, this facilitatory effect of NK1 receptor blockade on NA release was more pronounced than that on 5-HT and can be observed even after acute treatment (see section 3.1.1). Similarly, NK1 receptor knockout mice also show increased firing rate of locus coeruleus neurons [86] and a higher basal NA efflux in the prefrontal cortex than wild type controls [97, 98]. Notably, all these studies have investigated the effects of NK1 receptor activation or blockade on noradrenergic transmission under basal conditions. However, information regarding the effects of such interactions during situations where tachykinin pathways are highly activated, such as during aversive and stressful situations [99] would be even more relevant from a functional point of view. This issue seems particularly interesting as stress represents an important pathogenetic factor in many psychiatric disorders (see 2.1.1), and tachykinin antagonists have been shown to be particularly effective on "stressed" or pathophysiologically deranged systems [99, 100, see section 2.2.3]. Moreover, one should take into consideration that regulation of basal and evoked neurotransmitter release in a particular brain region may differ quantitatively and/or qualitatively, and effects on basal release may not generalize to effects on activated systems [101]. Indeed, we recently obtained evidence for such different modulation of NA release after NK1 receptor blockade as the administration of the selective NK1 receptor antagonist L822429 into the locus coeruleus enhanced basal, but attenuated stress-induced NA release in the prefrontal cortex [96]. Notably, similar attenuating effects on stress-induced NA release within the prefrontal cortex were also found after acute systemic administration of another NK1 receptor antagonist GR205171 [102]. Thus, these results suggest that therapeutic efficacy of NK1 receptor antagonists might be mediated by a suppressant rather than a stimulatory effect on stress-induced hyperactivation of NA neurotransmission.

Interaction with Dopamine

The localisation of tachykinin receptors on DA cells indicates possible interaction with DA function. Neurochemical studies have shown that in particular NK3 receptors have a modulatory influence on DA neurotransmission making this receptor a promising target for the development of novel antipsychotic drug therapy (see section 2.2.3) [103]. For example, local administration of the NK3 receptor agonist senktide into the ventral tegmental area and substantia nigra pars compacta enhanced extracellular DA efflux throughout their respective target areas, such as the nucleus accumbens, prefrontal cortex and striatum [104]. Similarly, electrophysiological data have demonstrated that NK3 receptor activation increases cell firing of midbrain DA neurons in rats and guinea pigs [105-107]. Moreover, agonist-stimulated cell firing of DA cells and subsequent DA efflux could be blocked by selective NK3 receptor antagonism [104, 106, 108]. Interestingly, acute systemic administration of the NK3 receptor antagonist SB223412 (talnetant) also produced a significant increase in extracellular DA efflux in the prefrontal cortex indicating a tonic inhibitory function of endogenous NKB on cortical DA release [108, 109]. However, although the mechanisms mediatiating this effect are not clarified yet it is unlikely that NK3 receptors located on DA cell bodies are involved in this mechanism because administration of NK3 receptor agonists directly to cell body areas enhanced DA release. Therefore, an indirect mechanism via activation of inhibitory (e.g. GABAergic) interneurons through NK3 receptors is more likely [108, 109]. Further studies are needed to examine this interaction more closely. From a functional point of view it will be important to investigate how NK3 receptors modulate DA release under stress conditions.

A close look at the role of NK1 receptors on frontocortical dopaminergic pathways reveals a more ambiguous and inconsistent picture. Previous studies have shown that blockade of NK1 receptors by administration of the selective NK1 receptor antagonist GR205171 increased DA release in the prefrontal cortex of rats [102, 110] suggesting a tonic inhibitory influence of NK1 receptors on DA function. This was confirmed by electrophysiological data demonstrating a dose-dependent enhancement of the firing rate of ventrotegmental dopaminergic neurones the major source of dopaminergic input to the frontal cortex after NK1 receptor antagonism [110]. However, a direct action on dopaminergic neurones is unlikely as microinjections of SP directly into dopaminergic cell body areas increased DA turnover in the frontal cortex [111, 112]. Notably, in line with such a facilitatory role of NK1 receptor activation are previous findings demonstrating an attenuation of the stress-induced DA turnover in the prefrontal cortex of rats and gerbils after NK1 receptor antagonism [102, 113]. Thus, further studies are necessary to clarify the role of NK1 receptors in dopaminergic functions.

2. THE SIGNIFICANCE OF TACHYKININ MECHANISMS IN ANXIETY, DEPRESSION AND SCHIZOPHRENIA

The rationale for an involvement of tachykinins in anxiety, depression and schizophrenia comes from both preclinical as well as clinical studies. First, tachykinins and their receptors are expressed in brain regions that are implicated in stress mechanisms and emotional processes such as hippocampus, frontal cortex, hypothalamus and amygdala (see sections 1.1 and 1.3). Second, tachykinin neurotransmission seems to be upregulated after exposure to distinct aversive and/or stressful situations in both animals and humans (see sections 2.1.1 and 2.2.1). Similarly, patients affected by stress-related mental disorders such as depression and anxiety disorders including post-traumatic stress disorder show evidence of increased tachykinin levels in the blood and brain (see section 2.2.2). Third, the central administration of tachykinins or analogue agonists produces a range of physiological and behavioral symptoms that are also induced after exposure to aversive and stressful experiences (see sections 2.1.2 and 2.2.1). In addition, tachykinin mechanisms regulate the release of other neurotransmitter systems such as 5-HT, NA and DA, which are known to be implicated in stress, mood and anxiety mechanisms (see sections 1.5 and 3.1.1). Finally, preclinical studies have shown physiological and behavioral changes in animal models of anxiety and depres-

sion after genetic or pharmacological inactivation of distinct tachykinin receptors resembling those seen with reference antidepressant or anxiolytic drugs (see section 2.1.2). Similarily, clinical efficacy of selective tachykinin receptor antagonists for the treatment of various stress-related disorders have been demonstrated in several studies (see section 2.2.3).

2.1. Preclinical Evidence From Animal Models

2.1.1. Altered Tachykinin Neurotransmission in Stressed Animals

Stress is known to be an important pathophysiological and precipitating factor in stress-related disorders such as depression and anxiety disorders, and contributes to relapses after periods of relative well-being [114, 115]. A variety of preclinical paradigms involving stress exposure have been developed to study pathways and mechanisms important in stress regulation, emotional and affective behavior [116-118] as well as providing test systems for the development of new therapeutic drugs including antidepressants [119-122].

Modulation of Stress Responses by Tachykinins

There is evidence that tachykinins may be involved in the modulation of stress responses in the brain. However, most studies so far investigating the role of tachykinins in stress mechanisms are focused on the SP/NK1 receptor system. For example, SP administered centrally in conscious rats induces a pattern of cardiovascular and behavioral responses which closely resemble the responses to various stressful stimuli [123, 124]. Moreover, there is also some evidence that tachykinins are involved in the regulation of the neuroendocrine stress response mediated primarily by the hypothalamo-pituitary-adrenal (HPA) axis. Recently, Mello and co-workers [125] have shown a potentiation of stress-induced corticosterone secretion after central injections of SP. This effect seems to be mediated by NK1 receptors, since pretreatment with a selective NK1 receptor antagonist prevented the SP effects. Moreover, Kakol-Palm and co-workers [126] have shown in gerbils that the stress-evoked plasma ACTH levels were blunted by acute administration of the NK1 receptor antagonist MK-869 (aprepitant) and almost completely prevented by saredutant, a selective NK2 receptor antagonist. In line with such a facilitatory role of these tachykinins found in rats and gerbils are further results from NK1 receptor knockout mice that showed lower stress-induced corticosterone secretion compared to wild type mice [127, 128]. However, though these data suggest a facilitatory role of these tachykinins on HPA axis activity, other studies do not confirm this role [129-131]. Thus, further research is needed to clarify the role of tachykinins on neuroendocrine stress responses.

Stress-Evoked Changes in Tachykininergic Neurotransmission

Additional evidence for the involvement of tachykinins in stress mechanisms comes from neurochemical studies investigating the effects of various stressors on intracerebral tachykinin levels. Altered SP levels were found after physiological and emotional stressors in various brain areas by different methods [132, 133] (Fig. (**3**)). Notably, measurements of the SP content in brain punches provided some inconsitent results, as both increased and decreased SP levels were found in discrete brain areas after stress exposure (Fig. (**3A**)). Alternatively, changes in the number of NK1 receptors may be used as an indirect measure of central SP release as NK1 receptors have been shown to undergo massive and rapid internalisation in response to various aversive and stressful stimuli *in vivo* [134]. After acute or chronic emotional and physiological stressors the number of membrane-bound NK1 receptors is reduced in several brain areas known to be involved in stress processing including the amygdala, septum, hypothalamus and locus coeruleus [135-142] pointing towards stress-induced changes in SP transmission. These effects are observed right after the stressor [136-140] as well as up to 21 days later [135, 142] and have also been shown to affect NK1 receptor gene expression levels [143-145]. Using this indirect way via changes in receptor expression, an involvement of the amygdaloid NKA/NK2 receptor, but not of the NKB/NK3 receptor system in stress responses has been demonstrated [142].

Nevertheless, both neurokinin tissue and receptor internalisation measurements are not adequate tools to detect dynamic changes in neuropeptide release [64, 132, 146]. Therefore, *in vivo* sampling techniques such as microdialysis or push-pull perfusion in combination with highly sensitive analytical measurements have been used more recently to monitor the effects of stress on the *in vivo* SP efflux in brain areas relevant in stress and anxiety mechanisms (Fig. (**3B**)). Using these methods, we demonstrated that emotional stressors such as immobilisation or forced swimming increase SP efflux in discrete brain areas such as amygdala [68, 99], septum [57], nucleus accumbens [147] and locus coeruleus [96]. The small size of the microdialysis probes and push-pull cannulae constructed in our laboratory allowed us to perfuse even subregions of single structures. We found stress-induced increase of SP release in the medial, but not in the central amygdala [99] and in the lateral part of the septum [57]. Our finding of high extracellular SP levels in limbic areas is consistent with immunohistochemical studies demonstrating a dense plexus of SP containing cell bodies and terminals in the medial amygdala [16, 20] as well as lateral septum [148, 149]. Interestingly, the enhanced SP release in the medial amygdala seems considerably more pronounced and prolonged after a severe emotional stressor (immobilization) than in response to a rather mild stressor (elevated platform exposure) indicating that the stress intensity is reflected by SP levels in these areas [99]. Interestingly, in the nucleus accumbens the stress-induced SP release was found to be under the inhibitory control of the transcription factor ΔFosB as viral overexpression of ΔFosB in SP neurons localised primarily in the periaqueductal gray suppressed the stress-induced SP release [147]. This effect could be associated with the antidepressant-like properties elicited by local NK1 receptor blockade within the nucleus accumbens [147]. This stress-induced activation of SP neurons within the periaqueductal gray is in line with previous studies demonstrating increased PPT-A expression [142] and SP-immunoreactivity in this area after acute stress exposure [150]. In addition to the periaqueductal gray acute stress exposure was found to increase mRNA levels of SP in the lateral parabrachial nucleus, a midbrain area implicated in the regulation of physiological and behavioral responses to aversive stimuli [151,

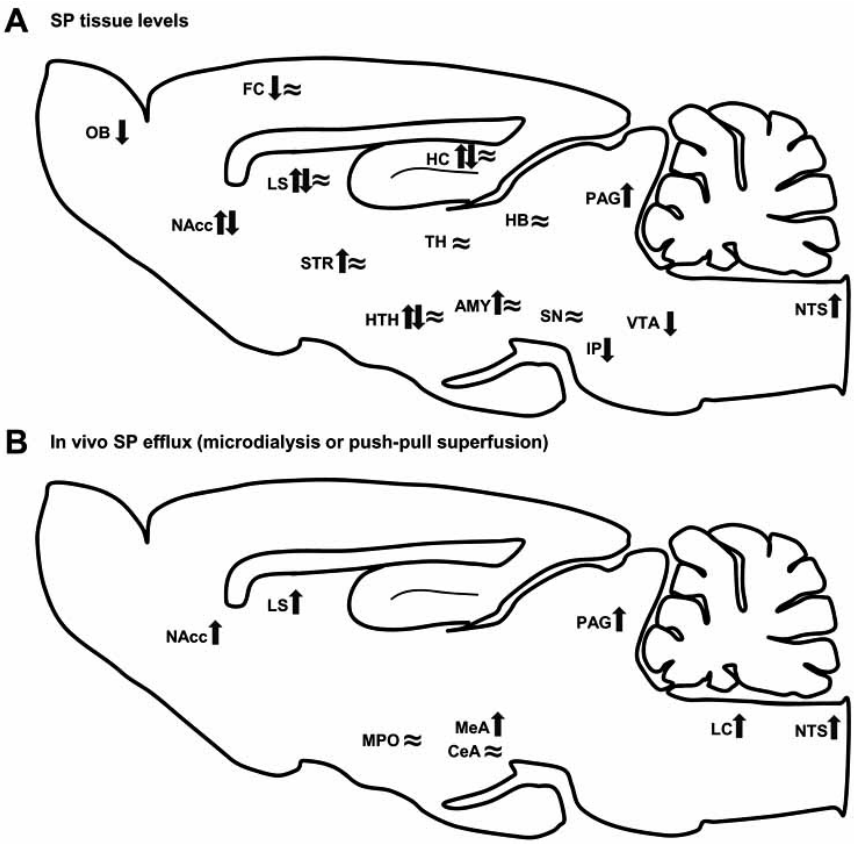

Fig. (3). Release of SP in distinct brain areas associated with emotional processing in response to various stressors. Increased (↑), decreased (↓) or unaltered (≈) SP levels were monitored by tissue measurements (**A**) or *in vivo* sampling methods such as microdialysis or push-pull superperfusion (**B**). Abbreviations: AMY, amygdala (CeA, central amygdala; MeA, medial amygdala); FC, frontal cortex; HB, habenula; HC, hippocampus; HTH, hypothalamus; IP, interpedincular nucleus; LS, lateral septum; LC, locus coeruleus; MPO, medial preoptic area; NAcc, nucleus accumbens; NTS, nucleus tractus solitarius; OB, olfactory bulb; PAG, periaqueductal gray; SN, substantia nigra; STR, striatum; TH, thalamus; VTA, ventral tegmentum area. Data summarized from references reviewed in [132, 133].

152]. As an integration site for autonomic regulation this area is anatomically connected to many brain regions of the stress circuitry such as amygdala and hypothalamic paraventricular nucleus [153, 154] and there is evidence that some of these projections contain SP [155-157]. However, the impact of these SP efferents from the lateral parabrachial nucleus in stress-activated SP transmission in forebrain areas such as medial amygdala has to be shown.

2.1.2. Dysregulated Tachykinin Transmission in Pathophysiological Animal Models

Alterations in tachykinin transmission were also found in different genetic animal models of pathological anxiety and depression. For instance, the congenitally 'depressed' Flinders Sensitive rats show higher SP and NKA tissue levels in the frontal cortex compared to the Flinders Resistant control rats [158]. Interestingly, in these rats maternal deprivation led to a marked increase in SP and NKA levels in the periaqueductal gray and various cortical areas [159]. Furthermore, in a recent study we also found that rats bred for extremes in high anxiety-related behavior (HAB) [160] show facilitated stress-induced SP release within the medial amygdala compared to their low anxiety (LAB) counterparts [161]. These data providing evidence for an upregulated SP neurotransmission in animal models of high anxiety and depression are in line with clinical findings of a disturbed SP neurotransmission in patients with stress-related diseases such as depression and anxiety disorders [162-164] (see section 2.2.2).

2.1.3. Behavioral Effects of Tachykinin Receptor Ligands in Animal Models

So far, most studies investigating behavioral effects of tachykinin ligands have focused on the SP/NK1 receptor system. For example, it is well documented that intracerebral injection of SP or adequate agonists induces aversive or anxiogenic-like effects while NK1 receptor blockade has antidepressant and anxiolytic-like effects in various species and in different behavioral tasks related to anxiety and depression such as elevated plus-maze, light/dark, social interaction, maternal separation, forced swim and tail suspension test [132, 165]. Since we have summarized behavioral effects of intracerebral injected NK1 receptor ligands in animal models of anxiety and depression in our previous review [132] we focus our attention here on other tachykinin receptors. Al-

though NK2 and NK3 receptors are becoming increasingly interesting as targets for novel pharmacotherapies (see section 2.2.3) there are only few studies investigating the role of these receptors in animal models of anxiety and depression. First evidence for a role of NKA and NKB in the control of stress and anxiety-related behavior comes from reports that intracerebral injections of NKA, NKB or adequate agonists modulate emotional behavior. For example, anxiogenic-like effects were found after central NK2 receptor activation in the elevated plus-maze and social interaction test [166, 167] (Table **1**). Since the discovery of the first non-peptidergic NK2 receptor antagonists [168, 169] several groups have started to investigate in preclinical studies whether stress and anxiety/fear-related behaviors can be modified by selective blockade of central NK2 receptors. Indeed, anxiolytic-like effects have been reported after selective NK2 receptor blockade in several animal models of anxiety such as elevated plus-maze test [167, 170-172], social interaction test [173, 174], light/dark test [175, 176] and mouse defense test battery [170, 177] (Table **1**). Notably, it seems that NK2 receptor antagonists exhibit anxiolytic-like effects in exploration-based tasks such as the light/dark, social interaction and elevated plus-maze test, but not in conflict-based procedures such as the punished drinking test [177], indicating that NK2 receptor antagonists have a specific profile of activity compared to drugs such as benzodiazepines, which are active in all of these procedures. In addition to their anxiolytic-like activity, NK2 receptor antagonists show antidepressant-like efficacy in the forced-swim test [138, 171, 178], in the maternal separation test [138, 173] and in the tonic immobility test [174]. However, though the best studied NK2 receptor antagonist, SR48968 (saredudant) is currently undergoing clinical evaluation in depressed patients (see section 2.2.3), little is known about the neurobiological mechanisms responsible for the anxiolytic and antidepressant-like activity of NK2 receptor antagonists. Notably, previous studies suggested that NK2 receptor antagonists produce some of their behavioral effects via the dorsal raphe nucleus because local infusion of different NK2 receptor antagonists produced anxiolytic-like effects [166, 179]. However, further studies are necessary to identify additional brain areas that may participate in the action of NK2 receptor mediated effects on emotional processes.

The effects of drugs acting at NK3 receptors on anxiety and depression-related behavior have been even less investigated. Early work in this field has suggested anxiolytic and antidepressant-like effects after NK3 receptor activation in various animal models [183-186] (Table **2**). For instance, in mice that were selected for over 43 generations for differences in opiod-mediated analgesia, the NK3 receptor agonist aminosenktide elicited an antidepressant-like effect in the forced swim test [184]. However, more recently anxiolytic and antidepressant-like effects have been reported in several animal models after NK3 receptor blockade [174, 178] (Table **2**). For example, an antidepressant-like effect of the NK3 receptor antagonist SR142801 (osanetant) was demonstrated that was similar in magnitude to that produced by selective NK1 and NK2 receptor antagonists or desipramine tested in the same experimental series [178]. Thus, it might be interesting to test whether a blockade of all 3 receptor types shows a potentiation effect. Furthermore, in gerbils intracerebroventricular administration of the selective NK3 receptor agonist senktide induced dose-dependent increases in foot tapping, a fear-related response, that was blocked by a selective NK3 receptor antagonist [180]. However, genetic deletion of NK3 receptors does not support a role for the NK3 receptor in anxiety and depression-related behavior because NK3 receptor knockout mice do not differ from wildtype mice in elevated plus-maze or forced swim test behavior [187]. However, functional compensation during development of conventional knockout mice can mask knockout phenotypes. Altogether, these data provide an incomplete picture about the role of NK3 receptors in emotional processes and further work will be necessary to clarify these conflicting results. Moreover, concerning the role of NK3 receptor antagonists as novel antipsychotics in the treatment of schizophrenia (see section 2.2.3) it is important to test these drugs in different animal models of schizophrenia including prepulse inhibition and latent inhibition test.

2.2. Evidence from Human Studies

2.2.1. The Role of Tachykinins in the Processing of Stress in Healthy Subjects

Only few experiments have been performed to examine the effects of stress on tachykinins in humans. SP plasma levels are reported to be increased in healthy control subjects under a mental stress condition using an arithmetic test [189] as well as in an Israeli population during missile attacks in the Persian Gulf War when levels of anxiety and anger were elevated compared to the pre- and post-hostility situation [190]. In contrast, neither the jump-stress in inexperienced parachutists [191] nor a diagnostic medical procedure [192] altered SP plasma levels in healthy subjects. Interestingly, a more detailed analysis of the sample in the two latter studies revealed that individuals with high anxiety scores compared to the rest of the group displayed higher SP measures throughout the investigations supporting a positive correlation between SP release and emotionality. Finally, compared to the resting control condition a clinically controlled psychosocial stress test involving a video camera, a free speech in a fake job interview and mental arithmetics in front of an audience (Trier Social Stress Test) [193] did not affect SP concentrations in blood and saliva [194]. These data do not provide a clear role of peripheral SP in stress responses. Rather, they suggest that only in a subset of people SP plasma levels are elevated in a stressor-dependent manner.

Here, the relevance of plasma SP for centrally mediated behavioral effects should be discussed since it has been a matter of debate for a long time whether peptides such as SP are able to penetrate the blood-brain barrier at all [195, 196]. The recent demonstration of central effects by peripherally applied SP [197, 198] supports the idea of an active transport mechanism for SP across the blood-brain barrier [199] and, thus, may allow some association between SP levels in serum and cerebrospinal fluid (CSF).

2.2.2. Altered Tachykinin Neurotransmission in Patients with Depression, Anxiety Disorders and Schizophrenia

Depression

Compared to control groups elevated levels of SP have been reported in the CSF, plasma or sweat of male and

Table 1. Behavioral Effects of Systemically or Intracerebrally Injected NK2 Receptor Ligands in Animal Tests of Anxiety and Depression

Drugs	Species	Site	Tests	Effects	Ref
NK2 Receptor Agonists					
NKA	Mice	ICV	Elevated plus-maze	Anxiogenic	[167]
	Mice	ICV	Elevated plus-maze	No effect [1]	[172]
[ß-Ala^8]NKA$_{(4-10)}$	Gerbils	ICV	Elevated plus-maze	Anxiolytic	[167]
GR64349	Rats	DR	Social interaction	Anxiogenic	[166]
	Gerbils	ICV	Hind foot tapping	No effect	[180]
	Gerbils	i.p.	Defecation	Anxiogenic	[126]
NK2 Receptor Antagonists					
SR48968	Rats	ICV	Elevated plus-maze	No effect [2]	[181]
	Rats	ICV	Noxious stress	No effect	[123]
	Rats	i.p.	Stress-induced defecation	No effect	[182]
	Rats	i.p./p.o.	Forced swim	Antidepressant	[138, 171, 178]
	Rats	i.p.	Elevated plus-maze	Anxiolytic	[170, 171]
	Rats	i.p.	Cat odor test	Anxiolytic	[170]
	Rats	i.p.	Social interaction	Anxiolytic	[173]
	Rats	i.p.	Passive avoidance	Antidepressant	[173]
	Rats	i.p.	Maternal separation	Antidepressant	[173]
	Rats	i.p.	Operant reinforcement	Antidepressant	[173]
	Rats	i.p.	Novel induced grooming	Anxiolytic	[171]
	Rats	i.p.	Punished conflict tests	No effect	[170]
	Mice	ICV	Elevated plus-maze	Anxiolytic	[167]
	Mice	ICV	Elevated plus-maze	Anxiolytic	[172]
	Mice	i.p.	Mouse defense	Anxiolytic	[170, 177]
	Mice	i.p.	Forced swim	Antidepressant	[138]
	Mice	s.c.	Light-dark test	Anxiolytic	[175, 176]
	Mice	i.p.	Elevated plus-maze	Anxiolytic	[171]
	Mice	i.p.	Chronic stress	Antidepressant	[173]
	Gerbils	p.o.	Social interaction	Anxiolytic	[174]
	Gerbils	p.o.	Tonic immobility test	Antidepressant	[174]
	Gerbils	i.p.	Stress-induced defecation	Anxiolytic	[126]
	Guinea pigs	i.p.	Maternal separation test	Antidepressant	[138]
	Marmosets	s.c.	Human intruder test	Anxiolytic	[176]
GR100679	Rats	DR	Elevated plus-maze	Anxiolytic	[166]
	Mice	s.c.	Light-dark test	Anxiolytic	[175]
GR115211	Rats	DR	Elevated plus-maze	Anxiolytic	[166]

(Table 1) contd….

Drugs	Species	Site	Tests	Effects	Ref
NK2 Receptor Antagonists					
GR159897	Rats	DR	Elevated plus-maze	Anxiolytic	[179]
	Rats	DR	Social interaction	Anxiolytic	[179]
	Mice	s.c	Light-dark	Anxiolytic	[176, 179]
	Marmosets	s.c	Human intruder	Anxiolytic	[176]
	Mice	s.c	Light-dark	Anxiolytic	[175]
SR144190	Mice	i.p	Mouse defense test	Anxiolytic	[177]

Abbreviations: DR, dorsal raphe nucleus; ICV, intracerebroventricular; i.p., intraperitoneal; p.o., per oral; Ref, references; s.c., subcutaneous.
[1] but blocked diazepam-induced anxiolytic effects.
[2] but blocked SP(1-6)-induced anxiogenic effects.

Table 2. Behavioral Effects of Systemic or Intracerebral Injected NK3 Receptor Ligands in Animal Tests of Anxiety and Depression

Drugs	Species	Site	Tests	Effects	Ref
NK3 Receptor Agonists					
NKB	Mice	ICV	Elevated plus-maze	No effect	[186]
Senktide	Mice	ICV	Elevated plus-maze	Anxiolytic	[172, 185, 186]
	Gerbils	ICV	Hind foot tapping	Anxiogenic	[180, 188]
Aminosenktide	Mice	i.p.	Forced swim	Antidepressant	[184]
NK3 Receptor Antagonists					
SR142801	Rats	i.p.	Elevated plus-maze	No effect [1]	[186]
	Rats	i.p.	Forced swim	Antidepressant	[178]
	Mice	ICV	Elevated plus-maze	No effect [2]	[185]
	Gerbils	p.o.	Social interaction	Anxiolytic	[174]
	Gerbils	p.o.	Tonic immobility test	Antidepressant	[174]
SB223412	Gerbils	i.p.	Hind foot tapping	Anxiolytic	[180]
$[Trp^7ß\text{-}Ala^8]NKA_{(4\text{-}10)}$	Mice	i.p.	Elevated plus-maze	No effect [2]	[185]
	Mice	i.p.	Elevated plus-maze	Anxiogenic	[186]
	Mice	i.p.	Elevated plus-maze	No effect [3]	[172]

Abbreviations: ICV, intracerebroventricular; i.p., intraperitoneal; p.o., per oral; Ref, references.
[1] but blocked senktide-induced anxiolytic effects.
[2] but anxiogenic effects after pretreatment with the opiod antagonist naloxone.
[3] but blocked diazepam-induced anxiolytic effects.

female patients with major depression [162-164, 200-202] (Table **3**) as well as in individuals suffering from depression-related syndromes including suicide attempters [203] (Table **3**), fibromyalgia syndrome [204] and chronic pain syndromes [205]. Interestingly, in healthy young men peripherally applied SP has been shown to worsen mood as indicated by an increased number of depressive symptoms [206]. In addition, major depression is accompanied by attenuated serum prolyl endopeptidase activity [207]. This enzyme degrades possibly SP and other neuropeptides such as arginine vasopressin (AVP), oxytocin or neurotensin pointing towards a reduced SP degradation in depression.

Nevertheless, SP levels have also been reported to be unaltered in the CSF [208-210] or plasma [209] in major depression or to be even lower in treatment-resistant depression compared to control groups [211] (Table **3**). The latter finding suggests that it may resemble rather the effect of chronic antidepressant or other psychotropic drug treatments for months or years than the effect of the psychopathology in this subgroup of depressed patients [211]. Yet, long-term

Table 3. SP Measurements in Patients with Depression, Anxiety Disorders and Schizophrenia in Comparison to Healthy Controls

	↑ SP	~ SP	↓ SP
Major Depression			
CSF	[162-164]	[208-210]	
Serum	[200-202]	[209]	
Sweat	[201]		
Treatment-resistant depression			
CSF			[211]
Suicide Attempters			
CSF	[203]		
Anxiety Disorders			
Post-traumatic stress disorder			
CSF	[162]		
Schizophrenia			
CSF		[163, 164, 220]	
Serum		[219]	
Brain (post-mortem tissue levels)			
Cortex		[221, 222, 225]	
Basal ganglia	[221]	[221, 222, 224, 225]	
Hippocampus	[222]	[225]	
Amygdala		[222]	[226]
Hypothalamus		[221]	
Thalamus		[222, 225]	
Substantia nigra		[224, 225]	
Temporal gyrus		[225]	
Neuroleptic treatment			
CSF			
Serum		risperidone [227]	haloperidol [227]
Brain (post-mortem tissue levels)			
Cortex	[225][1]	[221, 222, 225]	
Basal ganglia	[221]	[221, 222, 225]	
Hippocampus	[222, 225]		
Amygdala		[222]	
Hypothalamus		[221]	
Thalamus	[225][2]	[222, 225][3]	
Substantia nigra	[225]	[223]	
Temporal gyrus	[225][4]	[225][5]	

Abbreviations: ↑, increase; ~, no change; ↓, decrease; CSF, cerebrospinal fluid; SP, substance P.
[1] orbitofrontal cortex.
[2] anterior lateral nucleus, medial central nucleus.
[3] anterior thalamic nucleus, posterior lateral nucleus, dorsomedial nucleus.
[4] medial and inferior temporal gyrus. lateral occipito-temporal gyrus.
[5] superior temporal gyrus, insula.

treatment with various antidepressants including paroxetine, fluoxetine and mirtazepine or vagus nerve stimulation in treatment-resistant depression did not alter CSF or plasma SP levels in depressed participants [200, 206, 209-211] or suicide attempters [203]. However, when looking into some of these results in more detail, it became evident that SP serum levels in depressed patients were related to the response of these patients to antidepressant therapy [200, 206] with treatment-responders starting from higher serum SP levels compared to non-responders [206].

In post-mortem brain tissue of depressed individuals reductions of TAC1 mRNA in the lateral and basolateral amygdala [212] and of NK1 receptor expression in the orbitofrontal cortex [213] were observed while both markers of SP/NK1 receptor neurotransmission were unaltered in the amygdala, anterior cingulate or temporal cortices [212, 214, 215]. To note, reductions in TAC1 mRNA and NK1 receptor binding are both suggested to either represent a kind of negative feedback mechanism compensatory to increased SP release or to be related to antidepressant interventions in patients with mood disorders [212].

Anxiety Disorders

Compared to healthy control subjects, combat veterans with chronic forms of post-traumatic stress disorder displaying overlapping symptoms of depression also had elevated basal CSF SP levels [162] (Table **3**). Moreover, these levels were dramatically increased during the presentation of a symptom-provoking stimulus (combat video), but not during a neutral stimulus implicating central SP release in the mechanism of acute symptoms of post-traumatic stress disorder [162]. In support of this idea, exogenous SP elevated the symptoms of inner tension and of anxiety in healthy young men [197]. In the course of the recent methodological development of two PET ligands [^{11}C]GR205171 and [^{18}F]SPA-RQ which offers the possibility to image central NK1 receptors in human psychopathologies in a dynamic and non-invasive manner, Michelgard and co-workers [216] demonstrated reduced tracer uptake in the right amygdala of phobic patients during symptom provocation compared to baseline condition indicating increased SP release. Similarly, a widespread decrease of NK1 receptor binding has been recently reported also in patients with panic disorder compared to healthy controls [217] and the evaluation of NK1 receptor binding using PET imaging has been completed in patients with post-traumatic stress disorder but the data have not be released so far [218].

Schizophrenia

In drug-free individuals with schizophrenia and matched controls SP plasma and CSF levels did not differ [163, 164, 219, 220] (Table **3**). Central SP tissue levels were found to be elevated [221, 222], unaltered [221-225] and reduced [226] in the specific brain regions in schizophrenic patients (Table **3**). Given these inconsistent findings even in the same brain areas (Table **3**), it may be suggested that neuroleptic medication may have affected central SP levels. This idea is indeed in part supported by Toru and co-workers [225] demonstrating increased SP tissue levels in some specific brain areas including the cortex and substantia nigra in antipsychotic-treated vs. untreated patients while two other reports did not find any effect of pharmacotherapy [221, 222]. Moreover, it has been shown very recently that changes in SP serum levels may be neuroleptic-dependent [227] (Table **3**). In post-mortem brains of schizophrenic patients compared to healthy controls, TAC1 mRNA expression was reduced in the amygdala [212, 226], but not in the temporal cortex [212] or caudate putamen [228]. Using either in-situ hybridisation, quantitative receptor autoradiography or immunohistochemistry, increased densities of NK1 receptors were observed in the prefrontal cortex [59], caudate nucleus and nucleus accumbens [229] in schizophrenia while no changes were found in the cingulate and temporal cortices [212, 214] as well as in the amygdala [212, 230].

Taken together, information about tachykinins in stress-related human psychopathologies is limited or does not even exist in respect of the NKA/NK2 receptor and NKB/NK3 receptor systems. This is rather surprising given the first promising results in clinical trials with NK2 and NK3 receptor antagonists in depression/anxiety disorders and schizophrenia, respectively (see section 2.2.3). Regarding the SP/NK1 receptor system, there is no consistent evidence for clear dysfunctions in depression or schizophrenia while emerging, but not yet definitve evidence supports a role of SP in some forms of anxiety disorders. These inconsistent findings rather point towards an aberrant SP neurotransmission in a specific subset of individuals suffering from stress-related disorders. This population may especially benefit from drugs acting on the NK1 receptor. Therefore, it is essential that future research focuses on the understanding of how tachykinins, and not only SP, contribute to these psychopathologies including depression, anxiety disorders, and schizophrenia. For that purpose, modern neuroimaging tools such as PET or fMRI may be particularly helpful in order to investigate in which subgroups of depressed, anxious or schizophrenic patients neurokinin neurotransmission is indeed aberrant.

2.2.3. Efficacy of Tachykinin Receptor Antagonists in the Treatment of Depression, Anxiety Disorders and Schizophrenia

Depression

Varying outcomes of NK1 receptor antagonists in the treatment of depression are reported (Table **4**). In randomised, double-blind phase II trials the three different NK1 receptor antagonists MK869, L759274 and CP122721 reduced symptoms of depression in clinically diagnosed outpatients significantly more than placebo [136, 231, 232]. Moreover, the antidepressant effects of MK869 and CP122721 were similar to those of paroxetine and fluoxetine as comparators, respectively, but better in regard of adverse side effects. On the other hand, two other studies failed to demonstrate antidepressant actions of NK1 receptor antagonists as well as of active comparators over placebo making it difficult to interpret these negative findings [233, 234]. In contrast, subsequent large, placebo-controlled multisite phase III trials did not confirm the efficacy of MK869 despite near maximum receptor occupancy [235]. Consequently, Merck stopped its NK1 receptor antagonist program and several other pharmaceutical companies (e.g. Pfizer, Takeda-Abbott, Roche) followed Merck's decision despite first promising results while GlaxoSmithKline continued their program with two novel compounds (Table **4**).

Recently, the NK2 receptor antagonist SR48968 (saredudant) made it into clinical phase III trials for the treatment of major depression. The efficacy, safety and tolerability of saredudant up to 52-weeks treatment were evaluated in adult as well as elderly patients [236-242]. So far, two of the multicenter, double-blind placebo-controlled studies revealed positive results and their complete outcomes were expected to be on track for submission in the 3rd quarter 2008 [243]. Furthermore, a combination strategy of saredudant together with either paroxetine [243, 244] or escitalopram [243, 245] is also being assessed and participants are currently being recruited. Finally, the NK3 receptor antagonist SR142801 (osanetant) did not show clear efficacy at three different doses (50, 100 and 200 mg) in major depression vs. placebo and paroxetine in a 6-week phase IIb trial [246].

Anxiety Disorders

In the last years the interest of NK1 receptor antagonists has been particularly drawn on anxiety disorders (Table **4**). The reasons for that may be the in part disappointing results of NK1 receptor antagonists as antidepressant pharmacotherapies and the preliminary evidence of their therapeutic effectiveness in anxiety disorders combined with preclinical data available (see section 2.1.2). Chronic treatment with the NK1 receptor antagonist GR205171 has been shown to alleviate anxious symptoms in patients with social phobia during a stimulus-provocation task similarly to the SSRI citalopram and to a larger extent than placebo [247]. Interestingly, using PET this latter effect has been shown to coincide with attenuated stress-induced neural activity in the medial temporal lobe including the amygdala which has been ascribed a crucial role in the regulation of fear and anxiety [248, 249]. Similarly, increased [^{11}C]GR205171 binding in the right amygdala was correlated with reduced state anxiety ratings during symptom provocation in phobic patients suggesting that the acute anxiolytic effect of the NK1 receptor antagonist depended on the extent of receptor blockade achieved [216]. In further support, anxiolytic effects of the NK1 receptor antagonists MK869 and L759274 in the depressed sample with anxiety were evident [136, 232]. Currently, participants are recruited to test GR205171 vs. placebo in the treatment of post-traumatic stress disorder [250]. In addition, stimulated by data showing that the NK1 receptor antagonist GW597599 was able to reduce symptoms of CO_2-induced panic (described in [165]), a combination therapy of GW597599 and paroxetine in social anxiety disorder was initiated and has been completed [251]. Although the outcome has not been published yet, this combined approach was dropped from GSK's pipeline for anxiety as well as depression for unknown reasons [252]. Phase I and II trials have also been completed for the NK1 receptor antagonists GW823296 [253-255] and GW679769 [256] in the indication anxiety disorders, but the outcomes are not known so far. Regarding the two other neurokinin receptors, a phase II-study testing the efficacy and safety of the NK2 receptor antagonist SR48968 in patients with generalized anxiety disorder has been completed [243, 257, 258] whereas the NK3 receptor antagonist SR142801 had no therapeutic efficacy in patients with panic disorder [259].

Schizophrenia

In contrast to its inefficacy in depression and anxiety disorders, the NK3 receptor antagonist SR142801 has demonstrated positive actions in schizophrenia (Table **4**) pointing towards a new approach in the development of antipsychotics. Specifically, in a double-blind trial comparing four experimental compounds SR142801 caused a significantly greater improvement in positive symptoms and the measure of global clinical improvement than placebo at six weeks [260]. These effects were smaller, but not statistically significant different from those after treatment with the typical antipsychotic haloperidol. Moreover, of all the compounds tested, the percentage of patients completing the study was highest in the SR142801-treated group. Clincial phase II trials for the indication schizophrenia are completed with the NK3 receptor antagonist SB223412 (talnetant) [261-263], and according to a first financial report it was effective in improving positive symptoms and, possibly, cognition without any signs of severe side-effects [103, 264, 265]. It should be noted that both substances SR142801 and SB223412 do not have ideal pharmacotherapeutic characteristics due to pharmacokinitec problems including small bioavailability and reduced ability to cross the blood brain barrier [103, 108, 266]. The NK1 receptor antagonist MK869 did not prove efficacy as a primary therapeutic agent in acute psychosis in an exploratory clinical trial conducted in schizophrenic patients [233] and, to our knowledge, NK2 receptor antagonists have not been tested in schizophrenia so far.

Blockade of tachykinin receptors is a promising targeted approach in the treatment of stress-related disorders including depression, anxiety disorders and schizophrenia. Among these, the NK2 receptor antagonist SR48968 has to be particularly mentioned as it advanced into the latest stage of clinical phase III trials for the indication major depression and generalized anxiety disorder. NK1 receptor antagonists seem to recover (in particular for the indication anxiety) after their first hype and subsequent fall in 2005. Moreover, depressed individuals suffering from more severe forms or with moderate to high levels of anxiety seem to respond better to the antidepressant properties [136] as well as there are subgroups of depressed patients which show aberrant SP CSF and/or plasma levels. However, it became clear from inconsistent findings obtained during the development of NK1 receptor antagonists as potential antidepressant drugs that the blockade of distinct tachykinin receptors may not represent the ideal pharmacotherapeutic tool for all psychopathological patients, but for a specific subpopulation supporting the general idea of personalized treatment regimens for stress-related disorders. Alternatively, given that stress is often a precipitating or causative risk factor for many mental disorders (see above), a more general idea may be that the level of stress defines the responsiveness of the human patient population to neurokinin receptor blockade, in particular to NK1 receptors which is in fact supported by animal studies [99, 131]. Overall, these ideas go in hand with the claim for a better understanding of tachykininergic involvement in depression, anxiety disorders and schizophrenia as outlined before (see section 2.2.2).

3. NEW WAYS OF EXPLOITING TACHYKININ TARGETS IN MULTITARGET APPROACHES

3.1. Combining Tachykinin Targets with Targets of Established Therapeutics

Monoamine reuptake inhibitors acting predominantly at the 5-HT and/or NA transporter are currently first-line treat-

Table 4. Clinical Trials with Neurokinin Receptor Antagonists

Compound	Synonym	Receptor	Company	Phase	Comparator	Effect	Ref
Depression							
MK869	aprepitant	NK1	MSD	II	placebo paroxetine	yes	[136]
				II	placebo fluoxetine	failed	[233]
				III	placebo paroxetine	no	[235]
L759274		NK1	MSD	II	placebo paroxetine	failed	[165, 234]
				II	placebo	yes	[232]
GW679769	casopitant	NK1	GSK	II	placebo paroxetine	completed; unknown	[267, 268]
TAK637		NK1	Abbott Takeda	II		discontinued	[269]
CP122721		NK1	Pfizer	II	placebo fluoxetine	yes; discontinued	[165, 231]
GW823296	orvepitant	NK1	GSK	I		completed; unknown	[253-255]
R673		NK1	Roche	II		discontinued	[270, 271]
SR48968	saredudant	NK2	Sanofi	II	placebo	yes	[246]
				III	placebo	completed; yes/unknown	[236-243]
SR48968 + paroxetine	saredudant	NK2	Sanofi	III	placebo + saredudant	ongoing	[243, 244]
SR48968 + escitalopram	saredudant	NK2	Sanofi	III	placebo	ongoing	[243, 245]
SR142801	osanetant	NK3	Sanofi	II	placebo paroxetine	no	[246]
SSR146977		NK3	Sanofi	I			[246]
Anxiety Disorders							
GW823296	orvepitant	NK1	GSK	I		completed; unknown	[253-255]
CP122721		NK1	Pfizer	II		yes; discontinued	[133, 165]
Generalised Anxiety Disorder							
R673		NK1	Roche	II			[270]
SR48968	saredudant	NK2	Sanofi	III	placebo escitalopram	completed; unknown	[243, 257, 258]
Social Anxiety Disorder							
GW597599 + paroxetine	vestipitant	NK1	GSK	II	placebo	completed; discontinued	[251, 252]
GR205171	vofopitant	NK1	GSK	II	placebo citalopram	yes	[247]
GW679769	casopitant	NK1	GSK	II	placebo paroxetine	completed; unknown	[256]
Post-traumatic Stress Disorder							
GR205171	vofopitant	NK1	GSK	II	placebo	ongoing	[250]
Panic Disorder							
GW597599	vestipitant	NK1	GSK			yes in CO_2-induced panic	[165]
SR142801	osanetant	NK3	Sanofi	II	placebo paroxetine	no	[259]
Schizophrenia							
MK869	aprepitant	NK1	MSD	II	placebo haloperidol	no	[233]
SR142801	osanetant	NK3	Sanofi	II	placebo haloperidol	yes	[260]
SB223412	talnetant	NK3	GSK	II	placebo risperidone	completed; yes	[103, 261-263, 265]
SSR146977		NK3	Sanofi	I		unknown	[246]

Abbreviations: GSK, GlaxoSmithKline; MSD, Merck, Sharp & Dohme; Ref, references; Sanofi, Sanofi Aventis; unknown, outcome of the study not published yet.

ments for depression and a number of anxiety disorders [272-276]. These antidepressants which consist to the majority of SSRIs have a series of disadvantages most notably a delayed onset of therapeutic action and inadequate efficacy in a significant number of patients. Indeed, approximately 50% of depressed patients do not show an acceptable response to an initial antidepressant trial [277]. Moreover, many patients discontinue treatment with SSRIs and other monoamine reuptake inhibitors because of adverse side-effects including nausea, sexual dysfunction, and initial exacerbation of nervousness and anxiety.

The underlying idea of combining these established targets with novel targets is to exploit complimentary effects in order to boost efficacy, decrease delay to onset of action and counteract adverse side effects. As outlined below, there is promising evidence that at least part of these premises can be achieved by using NK1 receptor antagonist properties as an "add-on" to existing pharmacotherapy. This can be achieved either by combining individual drugs or using drugs with combined properties, e.g. mixed NK1 receptor antagonists/SSRIs [278, 279].

3.1.1. Add-On to Monoamine Reuptake Inhibitors

So far, the concept of combining tachykinin receptor antagonistic properties with inhibition of monoamine reuptake has been studied particularly for antagonism at NK1 receptors and 5-HT reuptake using different species including mice of different backgrounds, rats and gerbils (Table **5**). Support for possible complimentary action of this "add-on" target has been obtained from electrophysiological, neurochemical and behavioral studies. Since the clinical efficacy of SSRIs is based on facilitation of central serotonergic neurotransmission subsequent to blockade of the 5-HT transporter, the ability of NK1 receptor antagonism to further modulate 5-HT levels in relevant brain areas is of particular interest.

Evidence for Augmented Neurochemical Changes

The effect of SSRIs to increase extracellular 5-HT levels in the frontal cortex has been shown to be enhanced both after genetic or sustained pharmacological inactivation of NK1 receptors. Following NK1 receptor blockade, potentiated SSRI-induced increases in extracellular levels of 5-HT were found in the frontal cortex and additional brain areas including the amygdala, hippocampus, nucleus accumbens, striatum and dorsal raphe (Table **5**). This was demonstrated in different species and using different NK1 receptor antagonists. As most of the NK1 receptor antagonist actions were stereospecific, i.e. not expressed by the less active enantiomer, these effects can indeed be attributed to specific blockade of NK1 receptors [280]. Desensitization of inhibitory 5-HT_{1A} autoreceptors in the dorsal raphe and essential integrity of NA neurons (largely independent of 5-HT_{1A} receptors) have been identified as mechanisms contributing to the increased 5-HT activity by sustained NK1 receptor antagonism [88, 128, 281-283].

Acute administration of NK1 receptor antagonists does not seem to considerably elevate extracellular levels of 5-HT (see however below and 1.5), despite a facilitatory effect on dorsal raphe firing [283]. It was proposed that limited increases in firing of 5-HT neurons can be offset by 5-HT reuptake and/or the negative feedback action of terminal 5-HT autoreceptors and that the microdialysis technique used may not be sufficiently sensitive to pick up changes in terminal areas not particularly densly innervated by 5-HT fibers [88]. However, irrespective of these detection problems, the SSRI-induced effects on extracellular 5-HT levels in different brain areas are clearly potentiated by acute NK1 receptor antagonist treatment (Table **5**). This acute effect of NK1 receptor antagonists may be of particular interest concerning a possible faster onset of action of SSRIs (see below). Therefore an important question to ask is: what is the mechanism of this potentiating effect of NK1 receptor antagonism on 5-HT transmission? It has been shown that NK1 receptor antagonists have negligible affinities for 5-HT transporters and do not affect basal 5-HT uptake or the SSRI-induced inhibition of 5-HT uptake into synaptosomes [284]. This suggests that other mechanisms than interference with the 5-HT transporter protein are involved. Although acute blockade of NK1 receptors does not generally desensitise 5-HT_{1A} autoreceptors [88, 285, 286] and has no effect on the action of 5-HT_{1A} agonists *in vitro* [282], evidence for a reduction of the inhibitory influence of different SSRIs upon dorsal raphe firing was observed also after acute NK1 receptor antagonist treatment [280]. It was proposed that NK1 receptor antagonism limits the increases in dialysate 5-HT induced by the SSRI in the vicinity of serotonergic cell bodies in the dorsal raphe, thus, preventing the activation of the inhibitory feedback control exerted by somatodendritic 5-HT_{1A} autoreceptors [287]. The excitatory action of acute treatment with the NK1 receptor antagonist, RP67580, on 5-HT neuronal firing was no longer effective in NA-lesioned rats pretreated with the selective neurotoxin DSP-4 indicating that intact NA neurons are necessary for the modulatory interaction of NK1 receptor antagonism with 5-HT neuronal activity [88]. Furthermore, the acute effect of NK1 receptor antagonism on 5-HT neuronal activity has been proposed to involve additional, in particular GABAergic, glutamatergic and adrenergic mechanisms [33, 286, 288, 289]. These interactions do not necessarily involve interaction at the cell body level of 5-HT neurons, but may take place in other brain regions in close relation with 5-HT systems and expressing NK1 receptors such as lateral septum [57] (see section 1.5). Hence, there is evidence to suggest that the combination of NK1 receptor antagonists with SSRIs may elicit a regionally specific rise in 5-HT rather than a global boost affecting all brain areas similarly. However, this needs to be tested in more detail.

Apart from 5-HT, NK1 receptor antagonists modulate SSRI-induced changes in extracellular levels of additional monoamines including DA and NA (Table **5**). Given alone, NK1 receptor antagonists have been shown to activate the NA system (see section 1.5). Elevations in extracellular levels of NA in the frontal cortex have been demonstrated in NK1 receptor knockout mice and in response to NK1 receptor antagonists in the frontal cortex, amygdala and hippocampus, together with excitation of the locus coeruleus indicated by increased burst firing activity [88, 95, 96, 280, 285, 290] (see section 1.5). While Gobert and co-workers [280] have shown recently that the SSRI citalopram failed to increase NA levels in the hippocampus or frontal cortex, a large increase was noted after combination with the NK1

Table 5. Modulation of Neurochemical and Behavioral Effects of 5-HT Reuptake Inhibition by Neurokinin Receptor Antagonism (by Pharmacological or Genetic Inhibition)

Treatment SSRI + NK1 Receptor Antagonist	Species	Modulation of Effects (in %)							Ref
		SSRI-Induced Neurochemistry				Depression-Like Behavior[1] vs.		Anxiety-Like Behavior	
		5-HT	DA	NA	Brain Area	veh	Ineffective Dose of SSRI		
Acute NK1 Receptor Antagonist Treatments									
Paroxetine (4mg/kg)									
GR205171(10mg/kg)	Mice					-13	~ (-5)		[287]
	Mice	~			FC				[333]
GR205171 (30mg/kg)	Mice	+200			FC				[333]
	Mice					-12	~ (-5)		[287]
L733060 (40mg/kg)	Mice	+141			FC				[333]
Paroxetine (8mg/kg)									
GR205171 (10mg/kg)	Mice					-15	-9		[287]
GR205171 (30mg/kg)	Mice					-17	-11		[287]
Citalopram (0.63mg/kg)									
RP67580 (40mg/kg)	Rats	+114	~	~	FC				[280]
GR205171 (0.63mg/kg)	Gerbils							Anxiolytic[2]	[280]
GR205171 (10mg/kg)	Rats	~	+24	~	FC				[280]
GR205171 (20mg/kg)	Rats	+40	+46	~	FC				[280]
GR205171 (40mg/kg)	Rats	+81	+55	+40	FC				[280]
	Rats	+102	~		STR				[280]
	Rats	+126	~		NAcc				[280]
	Rats	+92		+33	dHC				[280]
	Rats	+150	+125	+68	BLA				[280]
Citalopram (2.5mg/kg)									
GR205171 (10mg/kg)	Rats							Anxiolytic[2]	[280]
GR205171 (40mg/kg)	Mice					-25	-20		[280]
Citalopram (4mg/kg)									
GR205171 (10mg/kg)	Mice					~(-8)	~(-2)		[287]
GR205171 (30mg/kg)	Mice					-19	-14		[287]
Citalopram (5mg/kg)									
GR205171 (10mg/kg)	Rats							Anxiolytic[3]	[280]
Citalopram (8mg/kg)									
GR205171 (10mg/kg)	Mice					~(-4)	~		[287]
GR205171 (30mg/kg)	Mice					-15	-9		[287]
Fluoxetine (10mg/kg)									
GR205171 (20mg/kg)	Rats	+105	~	~	FC				[280]
GR205171 (40mg/kg)	Rats	+152	+136	+97	FC				[280]

(Table 5) contd….

Treatment SSRI + NK1 Receptor Antagonist	Species	Modulation of Effects (in %)							Ref
		SSRI-Induced Neurochemistry				Depression-Like Behavior[1] vs.		Anxiety-Like Behavior	
		5-HT	DA	NA	Brain Area	veh	Ineffective Dose of SSRI		
Acute NK1 Receptor Antagonist Treatments									
Fluoxetine (40mg/kg)									
GR205171 (0.16mg/kg)	Gerbils							Anxiolytic[4]	[280]
Long-Term NK1 Receptor Antagonist Treatment									
Paroxetine (1mg/kg)									
GR205171 (10mg/kg) for 21d	Mice	+120			FC				[282]
	Mice	+50			DR				[282]
Genetic NK1 Receptor Inactivation									
Paroxetine (1mg/kg)									
NK1 -/-	Mice	+200			FC				[281]

Abbreviations: ~, no effect; 5-HT, serotonin; BLA, basolateral amygdala; DA, dopamine; DR, dorsal raphe nucleus; FC, frontal cortex; dHC, dorsal hippocampus; NA, noradrenaline; NAcc, nucleus accumbens core region; PFC, prefrontal cortex; Ref, references; SSRI, selective serotonin reuptake inhibitor; STR, striatum; veh, vehicle.
[1] immobility time in forced swim test.
[2] Reversal of anxiogenic effect in SI test.
[3] reduction of ultrasonic vocalizations.
[4] reversal of facilitation of fear-induced foot-tapping.

receptor antagonist GR205171. Moreover, GR205171 largely augmented the fluoxetine-induced rise in dialysate levels of DA and NA in the frontal cortex suggesting complimentary mood-elevating properties in addition to 5-HT [280]. This is an excellent example of the complimentary mechanism of action supplied by the combination of an established pharmacotherapeutic target with a novel one, the NK1 receptor.

Following the emerging "neurotrophic" theory of depression [84, 291], it was speculated that increased neurogenesis accompanied by increased neurotrophic factors/synaptic plasticity may contribute to the therapeutic efficacy of NK1 receptor antagonists in the treatment of depression [292]. Preclincical evidence suggests that NK1 receptor antagonists [293-295] as also SSRIs [296, 297] indeed target such mechanisms. However, whether there is a synergistic and/or complimentary effect of a combination of the two is not clear at present.

Evidence for Greater Efficacy and Faster Onset of Action

Since an increased availability of monoamines (in particular 5-HT) at nerve terminals is thought to be essential for the therapeutic activity of SSRIs, the neurochemical findings summarized in Table (**5**) would point to greater efficacy and possibly faster onset of action of SSRIs when combined with NK1 receptor antagonism. Indeed, behavioral evidence for this notion is provided in mice [287], rats and gerbils [280] (Table **5**). In Swiss mice a single systemic dose of GR-205171 (10 and 30 mg/kg, i.p.) had no effect by itself. However, it selectively potentiated the antidepressant-like activity of sub-active doses of the two SSRIs, citalopram (4 and 8 mg/kg) and paroxetine (4 and 8 mg/kg), but not that of the NA reuptake inhibitor, desipramine [287]. Interestingly, for the combination with paroxetine, the low dose of GR205171 was sufficient to produce a significant reduction in immobility while for the combination with citalopram the higher dose of GR205171 was needed to induce a significant effect [287].

It should be noted that the antidepressant action of NK1 receptor antagonists given alone seems variable in "normal" experimental animals. Mice genetically deprived of the NK1 receptor or the TAC1 gene display lower immobility times in the forced swim task than their wild-type controls [298] indicating a reduced depression-like behavior of these mice. In line with that, the NK1 receptor antagonist GR-205171 attenuated immobility time of mice [127, 299] and rats [178] which is interpreted as an antidepressant-like effect. On the other hand, the same antagonist was ineffective in two other studies in mice [287, 300]. Similarly, the NK1 receptor antagonists GW597599 (vestipitant) and L733060 proved to be ineffective while CP99994 was effective at a high dose only [300].

Evidence that NK1 receptor antagonists may induce faster therapeutic actions and effects complimentary to those of SSRIs comes from preliminary data obtained in a psychopathological animal model of enhanced anxiety and comorbid depression (HAB rats; see section 2.1.3) by using a functional imaging approach via evaluation of immediate early gene expression [301]. It was observed that different brain areas are activated by treatment with the SSRI paroxetine vs the selective NK1 receptor antagonist L822429. Furthermore, while paroxetine induced an antidepressant-like effect

in HABs after chronic, but not by acute treatment, L822429 induced this effect also after acute treatment [302].

Evidence for Reduced Side Effects of SSRIs

Enhanced Nervousness/Anxiety at Onset of Treatment

Acute SSRI treatment has been shown to elicit anxiogenic-like effects in animals [274, 303, 304] and humans especially in panic patients [305, 306] reducing compliance and triggering early drop outs of therapy. 5-HT_{2C} receptors in the hippocampus, amygdala and/or locus coeruleus have been suggested to mediate the anxiogenic actions of SSRIs [274, 307-309]. In contrast to SSRIs, acute treatment with NK1 receptor antagonists elicits anxiolytic effects in animals [132] and humans [216] opening the possibility that combination with NK1 receptor antagonists may abrogate the acute anxiogenic actions of SSRIs observed at the onset of therapy. Indeed, evidence for this proposition has been obtained in animal studies using different fear and anxiety tests, as well as combinations of different NK1 receptor antagonists and different SSRIs (Table **5**). Along these lines, vestipitant has been under clinical consideration in association with paroxetine for depression and anxiety disorders [252] (section 2.2.3; Table **4**).

Nausea and Gastrointestinal Discomfort

NK1 receptors are involved in the control of the vomiting reflex and in the induction of nausea. Blockade of these receptors has been shown to effectively suppress chemotherapy-elicited and post-operative emesis [310]. The clinical observation that NK1 receptor antagonists elicit minimal nausea as compared to paroxetine in depressed patients [136, 232] is consistent with this mechanism. Interestingly, in a small randomized, placebo controlled, double blind study in healthy subjects it was shown that the NK1 receptor antagonist aprepitant did not induce major changes in propulsive function of the gastrointestinal tract [311]. There is evidence that the adding of a NK1 receptor antagonist may reduce gastrointestinal discomfort elicited by SSRIs alone. Indeed, 80% of visceral primary afferents contain SP [312] suggesting that interference with SP transmission elicits beneficial effects upon nociceptive transmission from the gut. It has been shown recently that NK1 receptor antagonists inhibit stress-induced visceral pain responses and that this inhibition is even more pronounced following dual NK1/NK2 antagonisms [126].

Sexual Dysfunction

Treatment with the two NK1 receptor antagonists aprepitant and L759274 revealed no signs of adverse effects on sexual function. The incidence of sexual side effects was similar to placebo, but significantly lower compared to paroxetine [136, 232]. It is, thus, suggested that combination of the two targets would exert less disruption of sexual function at equipotent therapeutic doses.

3.1.2. Add-on to benzodiazepines

Benzodiazepines (BZDs) have been successfully used for short-term treatment of anxiety disorders (in particular generalized anxiety disorder and acute panic attacks) while long-term use is not recommended due to sedative side effects and increased risk of drug dependence. There is evidence that ligands interacting with neurokinin receptors can provide complimentary anxiolytic actions to BZDs, indicating that a combination approach may be helpful. For example, the NK2 receptor antagonist saredudant, but not diazepam was shown to remain active even shortly after acute stress [171]. The combination of these two targets may be even more attractive once subunit specific BZD drugs are available [313] in order to boost efficacy of the selective BZDs with expected lower side effect profile.

3.1.3. Add-On to Antipsychotics

First double-blind placebo controlled clinical trials have shown improvement of schizophrenic psychopathology including positive symptoms as well as lack of significant side effects by the two NK3 receptor antagonists osanetant and talnetant [103, 260, 265] (see section 2.2.3). Although these interesting findings need to be confirmed in larger studies, it appears that NK3 receptor antagonists may be useful as antipsychotic monotherapy or/and as add-on therapy to current antipsychotics [103, 109, 265]. The latter idea is supported by a recent animal study showing that the combination of the NK3 receptor antagonist talnetant with a low dose of the atypical antipsychotic risperidone augmented the risperidone-induced enhancement of DA in the prefrontal cortex [109]. To note, a dopaminergic hypoactivity in the frontal cortex and hippocampus has been related to negative symptoms and cognitive impairment observed in schizophrenic patients [314]. Since the effect of combined (low dose) risperidone and talnetant administration on cortical DA neurotransmission was comparable to that of the high dose of risperidone alone [109], it was suggested that this add-on strategy may be used to enhance tolerability (by using low doses) whilst maintaining or improving therapeutic efficacy of current antipsychotic drugs .

3.2. Combining Tachykinin Targets with Additional Novel Targets

Since currently prescribed first line drugs in depression and anxiety disorders have clear limitations (see above) drug discovery in this field has aimed at novel molecular targets that do not directly impact on monoamine systems but affect e.g. neuropeptide systems (e.g. AVP, corticotropin-releasing factor (CRF), SP, galanin, neuropeptide Y, neuropeptide S), excitatory or inhibitory amino acid systems (glutamate, GABA), or neurogenesis [272, 274-276, 315, 316]. A number of additional ligands have been developed for different candidate receptors including CRF1, AVP V1a, V1b, melanin concentrating hormone 1, galanin, mGLUR2, mGLUR5, AMPA, NMDA, $GABA_B$, and many more [315, 317-322].

In principle, combination approaches of tachykinin drugs with one or more of these new targets may be promising since it is likely that complimentary actions can be achieved by this strategy. However, the behavioral and neurochemical effects elicited by such combinations are just started to be investigated. First evidence for complimentary actions can be provided, for example, by identifying the neuroanatomical structures and circuits targeted by each of these drugs. Investigation of immediate early gene expression or cerebral glucose metabolism in wide areas of the brain can be used for this purpose, as it was shown for classical antidepressant treatments [323]. Unfortunately, while effects of pharmacol-

ogical interference with these novel targets on brain activation/metabolism have been investigated in part [302, 324-332], systematic studies directly comparing effects of drugs aiming at different of these novel targets, as well as investigating effects of their combination are missing so far. Combining such approaches with neurochemical and behavioral studies should help to reveal the potential of interfering with multiple of these novel targets including tachykinin targets.

CONCLUDING COMMENTS

A large body of evidence implicates tachykinins in the regulation of emotional processes. Neuroanatomical studies identified tachykinins and all three known tachykinin receptors in brain areas implicated in the pathophysiology of anxiety, depression and schizophrenia. Moreover, evidence suggests upregulated tachykinin transmission after aversive or stressful stimuli in both animals and human patients with various psychiatric disorders. On the other hand, preclinical studies have shown that blocking tachykinin transmission either by antagonists or genetic disruption attenuates the effects of stress including changes in neuronal activation, behavior and proliferation of (hippocampal) neurons. Based on these data, promising results in clinical trials have demonstrated efficacy of tachykinin receptor antagonist in the treatment of stress-related disorders such as depression, anxiety disorders and schizophrenia. Most intriguing were reports about NK1 receptor antagonists as novel and promising antidepressant drugs with a low side effect profile. Despite these initially encouraging clinical results, there were subsequent reports of negative outcome leading to disappointment and doubt of the idea that NK1 receptor antagonists may become effective antidepressants. However, since this time research continued and novel drugs with better pharmacokinetic and pharmacodynamic properties have been developed. At the moment, the most promising antidepressant drug is the NK2 receptor antagonist saredudant whose phase III trials have been recently successfully completed. Also NK1 receptor antagonists still have the potential to achieve clinical success in the treatment of anxiety disorders. Indeed, preliminary evidence from clinical studies shows therapeutic effectiveness of NK1 receptor antagonists in anxiety disorders including specific phobias and post-traumatic stress disorder. Furthermore, these drugs might be useful as adjunct therapy accelerating and/or potentiating the effects of established antidepressant drugs, in particular SSRIs. Finally, NK3 receptor antagonists seem to be promising drugs for the treatment of schizophrenia. There is evidence to suggest that tachykinin-related compounds reveal their greatest therapeutic potential in discrete patient populations. Appropriate patient selection however again depends very much on a better understanding of the mechanism(s) of drug action and underlying psychopathology. Given the evidence reviewed here, it may well be that specific patients with a pronounced stress-associated etiology would benefit most from treatments targeting tachykinin neurotransmitter systems. Much work remains to be done, in particular to enhance the understanding of the interaction of different tachykinins/receptors in emotional processing, the therapeutic potential of combined targeting of 2 or even all 3 of the tachykinin receptors, as well as combining these treatments with established medications to boost efficacy, and reduce the delay in therapeutic onset as well as unwanted effects.

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ABBREVIATIONS

AVP = Arginine vasopressin
BZD = Benzodiazepine
CRF = Corticotropin-releasing factor
CSF = Cerebrospinal fluid
DA = Dopamine
HAB = High anxiety-related behavior
HPA = Hypothalamo-pituitary-adrenal
5-HT = 5-Hydroxytryptamine
LAB = Low anxiety-related behavior
NA = Noradrenaline
NKA = Neurokinin A
NKB = Neurokinin B
NK1 = Neurokinin-1
NK2 = Neurokinin-2
NK3 = Neurokinin-3
PPT-A = Preprotachykinin A
SP = Substance P
SSRI = Selective serotonin reuptake inhibitor

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