Published in final edited form as:
CNS Neurol Disord Drug Targets. 2010 November 1; 9(5): 627–635.

The mammalian tachykinin ligand-receptor system: an emerging target for central neurological disorders

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Abstract

Our understanding of the complex signaling neurophysiology of the central nervous system has facilitated the exploration of potential novel receptor-ligand system targets for disorders of this most complex organ. In recent years, many relatively neglected receptor-ligand systems have been re-evaluated with respect to their ability to potently modulate discrete tracts in the central nervous system. One such system is the tachykinin (previously neurokinin) system. The multiple heptahelical G protein-coupled receptors and neuropeptide ligands that comprise this system may be significantly involved in more central nervous systems actions than previously thought, including sleep disorders, amyotrophic lateral sclerosis, Alzheimer's and Machado-Joseph disease. The development of our understanding of the role of the tachykinin receptor-ligand system in higher order central functions is likely to allow the creation of more specific and selective tachykinin-related neurotherapeutics.

Keywords

central neurological disorders; substance P; neurokinin A; neurokinin B; neurotherapeutics; receptor-ligand systems; tachykinin

INTRODUCTION

Tachykinin (TK) peptide neurotransmitters form a large functional group of signaling peptides in mammals, amphibia, mollusks, and invertebrates. This functional peptide group is typified, as the name implies, by possessing a potent and rapid muscular contractile action. These peptides have been demonstrated to control multiple and diverse physiological functions in these species. In each of the multiple species that employ these transmissive peptides, the actions of the ligand are mediated via activation of multiple and distinct isoforms of rhodopsin-like, heptahelical G protein-coupled receptors (GPCRs). Despite the ligands and receptors possessing intriguing and important functions in non-mammalian species, in this review we will concentrate on the potential usefulness of pharmacological manipulation of the TK receptor-ligand system for human disorders of a neurological origin. The goals of this review are to outline the roles that TKs play in various diseases and disorders of the central nervous system (CNS) and to present the data supporting the potential therapeutic avenues TKs provide.

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The authors have no conflicts of scientific interest with respect to the manuscript.

MAMMALIAN TACHYKININ PEPTIDES

Mammalian tachykinins, previously referred to as neurokinins, consist of a family of three primary functional peptides: substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), as well as four more recently classified peptides, *i.e.* neuropeptide K [1], neuropeptide γ [2] and hemokinin-1 [3]. As this review primarily concerns the therapeutic actions and relevance of tachykinins to neurophysiology, we will restrict our discussion to evidence implicating the three primary TKs, SP, NKA, and NKB, in pathophysiology. These were originally discovered in 1931 by von Euler and Gaddum [4] as an unknown potent stimulator of muscular contractile substance found in horse brain and intestine. SP was the first discovered TK and ignited a lengthy history of research of TKs [4]. SP was further studied and purified over the following 30 years with little success until the first molecular characterization of a TK peptide was uncovered in a structurally unidentified substance within the salivary gland of a Mediterranean octopus (*Eledone moschata*) [5]. The amino acid sequence of SP was only identified in 1971, forty years after its initial discovery [6]. In the following five years, two more peptides were purified and elucidated as TKs, after which a number of structurally or functionally related peptides were found throughout the CNS of various vertebrates and amphibians, including NKA and NKB. These peptides were discovered in the porcine spinal cord [7,8] and all contained a common COOH-terminal pentapeptide sequence Phe-X-Gly-Leu-Met-NH_2 [9]. In mammals the TK peptides are mainly expressed in neuronal tissue; therefore, in addition to their potent muscular actions, it appeared highly likely that TKs would possess important actions in the CNS. It is now well appreciated that the three primary mammalian TKs (SP, NKA, NKB) can all function as physiologically-relevant neurotransmitters/neuromodulators. The TK peptides are all amidated at their carboxyl terminus methionine. The amino acid sequence of SP, NKA, and NKB is identical in all mammals, but the sequence of hemokinin-1 appears to vary among mice, rats, and humans [3,10].

With respect to their molecular origin, all the mammalian TK peptides are derived from three discrete gene products: preprotachykinin A (PPTA), preprotachykinin B (PPTB), or preprotachykinin C. SP, NKA, neuropeptide K, and neuropeptide γ are all encoded by PPTA. NKB is the only TK encoded from the PPTB gene, while hemokinin-1 is produced from the PPTC gene [3,10]. As the expression of the PPTA/B genes is widespread, it is unsurprising that TKs are expressed in multiple organs (small and large intestine, lung, kidney, heart) as well as neuronal tissue. In tissues of neural origin, TKs are expressed primarily in the CNS, including the hypothalamus in mammals, although they are present in the peripheral nervous system (PNS) as well [11].

MAMMALIAN TACHYKININ RECEPTORS

The primary biological actions of the TKs are mediated through the activation of three distinct heptahelical GPCR isoforms. The receptor systems through which these ligands act are also well characterized [12–14]. In mammals, there are three primary TK GPCRs: TACR1, TACR2 and TACR3 receptors. These receptors share between 40–50% identity at the amino acid level [11]. Each receptor demonstrates a preferential affinity for one of the TK peptides, *i.e.*, SP-TACR1, NKA-TACR2, NKB-TACR3. All three peptides, however, can act as full agonists at each of the three receptors, although their potency order mimics their affinity specificity, *i.e.*, SP is the most potent at TACR1, NKA is the most potent at the TACR2, and NKB is the most potent at the TACR3 receptor. Each of the three TK GPCRs can be effectively coupled to multiple intracellular signaling systems (adenylyl cyclase, phospholipase C-beta, calcium-dependent potassium channel modulation, transient receptor potential channel modulation to exert their eventual cellular effects [13,15–18]. As the majority of the ligand and receptor components of the TK system are highly enriched in the CNS, we will dedicate the majority of this review to investigating the roles of the TK system in complex neurological disorders.

TACHYKININS AND CENTRAL NERVOUS SYSTEM DISORDERS

I. AFFECTIVE DISORDERS

Affective disorders are characterized by a consistent, pervasive alteration in mood and affecting thoughts, emotions, and behaviors. Affective disorders include depression, anxiety, and bi-polar disorder. In recent years, there has been a plethora of data indicating the involvement of tachykinins, particularly SP, in affective disorders [19,20]. A number of approaches has been utilized to study the role that SP plays in the etiology of human affective disorders, including the measurement of serum levels in depressed as well as anxious patients, infusion of SP into otherwise healthy patients, and measurement of SP levels in patients suffering from depression. Schedlowski and colleagues [21] as well as Weiss and colleagues [22] demonstrated that subjects with high anxiety generally displayed higher plasma levels of SP than their low anxiety counterparts. In a 2003 study examining the SP levels of patients suffering from depression, Bondy and colleagues found that patients diagnosed with acute depression had significantly and consistently higher SP levels than their control counterparts over a four-week period [23]. In addition to studies of plasma levels of TKs, cerebrospinal fluid (CSF) levels of SP have also been directly correlated with depression [24]. Interestingly, it has also been shown that there is a direct correlation of CSF SP levels with the presence of schizophrenic symptomology [24]. Reinforcing the argument for the involvement of SP in depression, numerous additional studies have also reported significantly elevated levels of CSF SP in patients with fibromyalgia syndrome [25–27], a disorder that is strongly associated with depression [28]. Interestingly, infusion of SP during sleep has been shown to significantly worsen mood upon wakening, as well as decrease the quality of sleep. Subjects given intravenous infusions of SP displayed an increase in REM latency, increased stage 1 sleep, and longer time awake, all objective measurements of decreased sleep quality [29]. It appears, therefore, that TK ligands are phenomenologically and functionally linked to the control of affective phenotypes in a complex manner.

II. AMYOTROPHIC LATERAL SCLEROSIS AND MOTOR NEURON DISEASE

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the progressive loss of motor neuron function, primarily via neuronal oxidative mechanisms. Associations between ALS and TKs were first investigated by Gillberg and colleagues in 1982 [30]. In the spinal cord of ALS and control patients, some distinct perturbations in the numbers of SP-positive cells were noted. Matsuishi and colleagues demonstrated an important connection between TKs and ALS etiology [31]. When CSF SP levels were measured in ALS patients and controls, no significant differences were found; however, when the researchers investigated differences in SP levels within the ALS subjects, it was found that patients who presented with ALS for fewer than 2.5 years had significantly higher levels than patients who had been afflicted for greater than 2.5 years. It was hypothesized that in this context, SP may be acting as a neurotrophic factor that is elevated in order to compensate for the degeneration of the anterior horn cells that occurs in ALS. In addition to ALS, perturbations in the TK system have also been shown to play a role in related disorders, such as adult-onset motor neuron disease with basophilic inclusions (MND/BI). Significant reductions of SP-immunopositive cells have been demonstrated in the substantia nigra of MND/BI patients compared to control subjects [32].

III. EPILEPSY

Multiple forms of epilepsy exist, and they are differentiated upon the type and severity of presented symptomology. One of the most debilitating forms of epilepsy is status epilepticus (SE). In SE, seizures occur in the form of a series of protracted episodes that can last for prolonged periods of time and can thus be fatal if episodes merge with each other and immediate treatment is not available. Both SP, and NKB to a lesser extent, have been implicated as possible

causal factors in the generation of SE [33]. When injected into the rat hippocampus, SP can significantly lower, in a dose-dependent manner, the initiation threshold for seizures induced by perforant path stimulation (PPS) [34]. It was subsequently demonstrated that spantide II, a substance P receptor antagonist, was able to both suppress electro-encephalogram (EEG) spike frequency as well as prevent the development of SE induced by the PPS protocol. Additionally, reinforcing an important role of TKs in SE, genetically-ablated PPTA(−/−) mice display significantly higher resistance to seizures induced by kainate injection. The PPTA(−/−) mice have been shown to experience seizures of shorter duration and lower intensity, as well as recover more rapidly from episodes. Wild-type mice given the same dose of kainate exhibited many neurons with acidophilic cytoplasm and shrunken, pyknotic nuclei in the hippocampus [35]. These data indicate a pro-convulsant role for the PPTA gene and thus SP and NKA as well.

IV. CENTRAL MOVEMENT DISORDERS

The mammalian TK system has been implicated in several centrally-based neurological movement disorders that share the commonality of nigrostriatal degeneration. SP and NKB are both are expressed in D_1R-containing striatal neurons [36–39]. SP is co-localized with dynorphin and D_1Rs in striatonigral neurons [38], whereas NKB is co-localized with D_1Rs in a unique population of striatal projection neurons [39,40]. TAC1Rs are highly expressed in many brain regions involved in motor control, including dopaminergic regions of the striatum [41,42]. TACR3 receptors are moderately expressed in the brain but are concentrated in GABA interneurons in striatum and in dopamine neurons of substantia nigra [43–46]. Therefore, it is not surprising that pharmacological TK-system targeting of central dopaminergic disorders is gaining interest [47–49].

Parkinson's disease (PD) is a neurodegenerative motor disorder characterized by rigidity, bradykinesia, and resting tremor. The primary cause of PD is a degeneration of dopamine neurons within the substantia nigra and basal ganglia. Multiple studies have uncovered a correlation between the onset of PD and the degeneration of neurons containing SP throughout the substantia nigra and basal ganglia, as well as in surrounding areas. The human pedunculopontine tegmental nucleus (PPTN) is associated with movement [50], and neurons within the PPTN have been shown to contain SP [51]. Analysis of SP-containing neurons within the PPTN (as well as the laterodorsal tegmental nucleus and the oral pontine reticular nucleus) of deceased subjects with no apparent neurological disease showed that subjects diagnosed post-mortem with PD had severely damaged SP-positive neurons. It was also shown that the older post-mortem PD patients possessed the least total SP-positive neurons in the mesopontine tegmentum [52], suggesting SP neuron-specific progressive degeneration. Similar findings have been reported regarding the status of SP-positive neurons in the dorsal motor vagal nuclei [51], the globus pallidus [53], and the substantia nigra [53,54] of human post-mortem PD brains. In an attempt to elucidate the role of SP in PD, Cui and colleagues examined the involvement of the pallidal SP system in PD by observing the electrophysiological effects of SP on pallidal neurons of 6-OHDA-lesioned rats [55]. Neurons in the globus pallidus exposed to SP demonstrated a smaller increase in firing rate in 6-OHDA-treated rats than in control rats, indicating a decreased expression of functional TACR1s in the globus pallidus in the PD model. They also found that a selective TACR1 antagonist blocked SP-induced excitation, suggesting the involvement of TACR1 receptors in modulating electrical activity in the globus pallidus of PD patients [55]. The 6-OHDA-lesion rat model has also been used to analyze the role of NKB-TACR3 system in PD [56,57]. After 6-OHDA lesioning, NKB mRNA expression was increased and could be even further enhanced after the lesion by repeated L-DOPA treatment. In contrast to NKB levels, the expression of SP mRNA decreased after the lesion [57]. From this study, it is apparent that in contrast to SP, dopamine regulates NKB mRNA in a bidirectional manner [57]. The potential to develop TK-based therapeutics to treat PD has

not been overlooked. In fact, numerous studies have reported DA neuron growth in response to intracerebroventricular (i.c.v.) administration of SP [58], as well as TACR1 and TACR3 agonists [59].

Machado-Joseph disease (MJD), also known as Nigrospinodental Degeneration (ND) or spinocerebellar ataxia type 3 (SCA3), is a neurodegenerative disease with symptoms reminiscent of PD [60]. MJD is the most common type of autosomal dominantly-inherited cerebellar ataxias in Europe, Japan, and the United States [61]. MJD is believed to be caused by a CAG expansion in the SCA3 gene located on chromosome 14q32.1 and is characterized by poor motor control. Based on previous anatomic, biochemical, and pharmacological studies associating SP with dopaminergic neurons in the substantia nigra and the striatum [62–64], Matsuishi and colleagues conducted a study comparing the CSF SP levels of 7 subjects with MJD to 14 controls. They found that the level of SP within the CSF of patients with MJD was significantly lower than the levels observed in the control patients. Despite these promising findings, however, no correlations were found between the CSF level of SP and the presence or absence of clinical symptoms such as disease duration, severity, type, or treatment, or clinical symptoms of peripheral nerve involvement or signs of autonomic dysfunction [65]. The authors posited that these findings could reflect a decreased concentration of SP in the neurons, which may be indicative of the involvement of the peripheral nerves or the dorsal root ganglia, which is characteristic of MJD.

V. TRAUMATIC BRAIN INJURY

Recent studies have suggested that SP, as well as a number of other neuropeptides, may play a substantial role in the functional and morphological degeneration following acute injury in both the peripheral nervous system (PNS) and CNS [66]. Acute traumatic brain injury (TBI) results in the generation of neurologic deficits through two primary mechanisms [67]. The primary injury occurs at the time of the trauma and includes mechanical processes, such as shearing, laceration, and stretching of nerve fibers. Secondary injury occurs at later time points and is composed of biochemical and physiological factors that are initiated by the primary event and manifest over time [67]. Morbidity after brain injury is strongly associated with the development of this secondary injury cascade. Secondary injury factors include blood–brain barrier rupture, edema, release of excitatory amino acids, disrupted ion homeostasis, oxidative stress, and metabolic failure [67–69]. It is well known that edema is highly related to outcome after injury; however, the mechanisms associated with the formation of edema are still unclear. With respect to peripheral tissue edema, an association between neuropeptides and the development of increased vascular permeability and edema is evident and has been generically termed ‘neurogenic inflammation’ [70]. Neurogenic inflammation is a neurally elicited reaction that involves vasodilation, increased microvascular permeability, protein extravasation, and tissue swelling. Studies of peripheral nerves have shown that neurogenic inflammation is the result of stimulation of C-fibers, which express several neuropeptides, including SP and NKA [71,72]. Trauma-induced, uncontrolled edema formation in the CNS elevates intracranial pressure, which can cause disruption of cerebral blood flow. This vascular compression can lead to reduced perfusion, localized hypoxia and ischemia, and eventual neuronal death. Therefore, it is of particular interest to pharmacologically attenuate or inhibit such inflammation after TBI. Malcangio and colleagues have demonstrated that SP is released in the nervous system following peripheral nerve injury (by measuring SP expression in axotomized large afferents) and is downregulated in small fibers following stimulation of Aβ-fibers and Aβ/Aδ/C-fibers [73]. SP release in the thoracic spinal cord has also been directly measured following focal traumatic injury [74]. Perivascular SP immunoreactivity has been shown to increase following TBI, and this was irrespective of the severity of the injury and occurred in both focal and diffuse injury models [75]. Therefore, one of the potential therapeutic mechanisms that could be exploited for the treatment of TBI would be receptor antagonism

directly after the initial trauma [76–78]. These therapeutic endeavors will be discussed in greater detail later in this review.

VI. ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a common form of pre-senile dementia that is dominantly characterized by progressive memory loss, as well as cognitive and linguistic impairments. AD is one of most prevalent diseases in Westernized countries, and an efficacious treatment strategy represents one of the most important challenges in modern medicine [79,80]. The physiological mechanisms leading to the generation of AD pathophysiology are complex and multifactorial [81–83]. However, there is a general consensus that post-translational alterations in the cytoskeletal protein tau as well as changes in amyloid precursor protein processing are pivotal. The primary sites of these molecular pathologies are the hippocampus and cortex, although other brain regions can be subsequently affected. Although a correlation between TKs, in particular SP, and AD is well documented [84,85], most studies indicate that SP is not a causal factor in the development of AD. Several studies have documented a decrease in SP immunoreactive tissue in various regions of AD brains, *e.g*., significant reductions in SP-positive cells are found in the midfrontal, inferior parietal, and occipital lobes, as well as the superior and inferior temporal gyri [86]. Similar studies have shown decreased SP-positive cells in the frontal and occipital cortices, as well as the isocortex, hippocampus, and to a lesser extent, the allocortex [84,87–89]. In addition, substance P-immunoreactive profiles coexist within single senile amyloid-containing plaques of patients with AD [90]. Despite parallels between AD pathology and the presence of SP, there is a relative scarcity of evidence that SP plays a prominent role in the development of AD [91,92]. In a study of five distinct CSF biomarkers, no significant difference between AD and healthy patients with respect to SP immunoreactivity has been observed [93]. However, within AD subjects, patients with late onset (>65 years old) AD had significantly higher levels of SP than both patients with earlier onset AD and control patients [93].

With respect to a potential mechanistic connection between SP and cognitive function, it has been demonstrated that expression of SP, NKB, and the TACR1 is especially high in brain regions critical for the regulation of emotion and cognition [94,95]. The SP ligand system functionally interacts with the cholinergic ascending system of the nucleus basalis Meynert, which is one of the main neuronal pathway deficiencies observed in AD. Recreation of the AD pathology with ibotenic acid infusion into the rat nucleus basalis magnocellularis, can induce significant reductions in SP levels in the frontal cortex and striatum [96]. Conversely, injection of SP into the nucleus basalis magnocellularis has been shown to increase acetylcholine levels in the hippocampus and cortex of rats in a TACR1-dependent manner [97,98].

VII. HUNTINGTON'S DISEASE

Huntington's disease (HD) is a genetically linked neurodegenerative disorder first described by George Huntington in 1872. It is a hyperkinetic disorder specifically characterized by autosomally-dominant heritability; presentation of chorea or jerky, dance-like movements; behavioral and physical disturbances, including personality changes and skewed balance; cognitive impairments, such as depression or dementia; and death 10–15 years after initial onset [99,100]. HD is equally frequent in men and women, and its incidence in the whole population is approximately 5–10 cases per 100,000 worldwide, making it the most common inherited neurodegenerative disorder [101]. The primary cause of the disorder was identified as an expanded trinucleotide repeat (CAG) in the gene encoding for the huntingtin protein (*htt*). It is interesting to note, however, that in addition to the archetypical neurological phenotypic attributes, many HD patients develop a specific form of genetic diabetes and experience extreme weight loss, which is mirrored in animal models of the genetic disorder [102].

As with several other neurodegenerative disorders, SP is generally found to be decreased in subjects diagnosed with HD. HD is generally characterized by neuronal loss in the striatum [103], including severe losses in the dorsal caudate nucleus and putamen [104,105]. Multiple studies have addressed the loss of SP-positive neurons throughout the striatum and other regions of the basal ganglia, including the internal pallidal segment of the globus pallidus and the substantia nigra [106]. In a study of the differential sparing of compartments in the striatum of HD patients, as related to the distribution of SP, Ferrante and colleagues found a dorsoventral gradient of SP immunoreactivity loss in the striatum that was directly correlated with the severity of the disease. The most severe cases of HD showed very little to no staining for SP in the caudate nucleus and dorsal putamen, whereas the absence of SP in cases of moderately severe HD was less extensive [104]. This loss of SP indicated a reduction of intrinsic spiny neurons which project to the globus pallidus and substantia nigra [103], which are known to be preferentially affected in HD [107]. Additionally, a correlation between classical HD pathology and TK levels has also been demonstrated in an HD-related condition, *i.e.*, 'HD phenocopy'. Phenocopies of HD are individuals with a family history, clinical symptoms, and occasionally pathological evidence of HD who do not possess the expanded CAG repeat within the huntingtin (*htt)* gene. HD phenocopy patients often present with selective loss of preprotachykinin neurons and dysfunction of surviving preprotachykinin neurons within the striatum. In addition to this disruption, HD phenocopies also demonstrate a profound loss of immunohistochemical staining for SP in terminals of striatal neurons projecting to the substantia nigra [106].

TACHYKININ NEUROTHERAPEUTIC MECHANISMS

As we have seen, there is considerable evidence linking alterations of the TK ligand and receptor system in multiple central neurological disorders. It is clear that with respect to these diseases, manipulation of the TK receptor-ligand system may prove beneficial either by stemming the progression of the disorders or through a direct therapeutic mechanism. In the next section of this review, we will delineate the molecular and neurophysiological mechanisms by which modulation of the TK receptor-ligand system may yield significant therapeutics actions. These mechanisms include actions that can repair, protect, or even replace neural tissue damaged either by congenital disease or trauma.

I. NEUROTROPHIC MECHANISMS

The ability of SP to promote neuronal growth is a well-documented phenomenon. In recent times, the concept of adult neurogenesis has been promoted as a potential mechanism by which damaged neuronal tissue can be replaced by activation and development of neural progenitor cells. In a study designed to measure the effects of SP on the rat cortical subventricular zone (SVZ) and the hippocampal dentate gyrus (DG), which are areas known to possess a neuronal stem cell population, it was found that with the introduction of SP, there was a significant increase in the number of neural progenitor cells (NPCs) in the rat SVZ and DG [108]. Central nervous system neurogenesis has also been studied in TACR1(−/−) mice. These mice demonstrate significantly elevated levels of neurogenesis in the DG compared to control mice [109]. This increase in neurogenesis, however, seems to be strain-dependent, as genetic ablation of TACR1 in a B6 strain failed to potentiate adult neurogenesis, while in a 129B6 strain background, the increase in neurogenesis [109] was replicated [110]. These two strains differed in the level of plasma corticosterone, suggesting a potential link between the TK-control of neurogenesis and stress-response mechanisms. With both ligand stimulation and receptor expression levels controlling NPC levels in a complicated manner, it seems likely that the future manipulation of the TK system may be employed to control the replacement or the rejuvenation of central nervous tissue.

II. NEUROINFLAMMATION

Inflammatory responses within the CNS are often the result of traumatic injury and infectious agents [111]. Inflammation, while often representative of a protective immune response, may also result in progressive damage to the CNS. There is significant evidence to indicate that SP is a major component of the inflammatory responses at peripheral sites, as well as CNS cell types. Therefore, the ability to specifically control TK-related activities in central inflammatory responses may represent an important pharmacotherapeutic mechanism for centrally acting TK drugs. Numerous studies have shown that astrocyte-derived SP may activate several transcriptional regulators that play an important role in the regulation of pro-inflammatory molecule expression. For example, NF-κB [112,113] and p38 MAP kinase [113] have both been shown to be activated by SP in central nervous tissue. Both SP and its cognate TACR1 receptor are also known to be expressed at high levels in murine microglia [114,115] and are thought to play a role via NF-κB activation in the production of the pro-inflammatory cytokines TNF-alpha, IL-1, and IL-6 [116–118]. In addition to the neuroinflammatory-promoting properties of SP, NKA has also been associated with the inflammatory cytokines IL-1 [119] and IL-6 [120]. It is important to note, however, that some studies suggest that SP alone is not sufficient to elicit neuroinflammatory immune responses and that it must work with other microglial responses to inflammatory stimuli [116,121].

III. NEUROPROTECTION

Neuronal tissue can be severely damaged either through physical trauma or excitotoxic insults. Both of these processes can result in calcium overload, protein degradation, or DNA damage. There are endogenous cellular responses that can be activated by neuronal tissue in response to damage that attempt to protect cellular, protein, and nucleic acid integrity. There is a large variety of endogenous neuroprotective signaling mechanisms that can be mimicked by pharmacotherpeutics to ameliorate CNS insults. As with many forms of activity of neuromodulators in the CNS, there are instances in which TKs have been implicated as players in a number of physiological and pathological conditions (*e.g*., the pro-convulsant role of the PPTA gene [35] and the involvement of SP in TBI [73–75]), but there are also numerous illustrations of the neuroprotective qualities of TKs both *in vitro* and *in vivo*. For example, multiple TK agonists are able to protect cerebellar granule cells from neuronal cell death induced by serum and potassium deprivation. These neuroprotective effects of SP have been found to be mediated by activation of the kinases Akt-1 and extracellular signal-regulated kinase (ERK) [122]. Similar protective actions of TKs acting at the TACR1 have been seen in dissociated spiral ganglia when they were exposed to trophic factor deprivation shock [123]. In contrast to the activation of protective kinases, such as Akt-1, the neuroprotective action of TK was mediated via a TACR1-dependent inhibition of pro-apoptotic caspase enzymes. While many studies have concentrated on the neuroprotective abilities of SP, other mammalian TKs also display such beneficial activity. Hence, when SP was unable to protect striatal cholinergic neurons, NKA and NKB were more potent at protecting the neuronal cells from an excitotoxic (kainic acid) insult [124]. As cholinergic pathways have been demonstrated to play a crucial role in cognitive decline and AD, it is important to note that SP was recently demonstrated to protect cerebellar granule neurons from amyloid beta (A_β)-mediated cytotoxicity [125]. This action of SP was thought to occur via an SP-mediated downregulation and functional inhibition of specific voltage-gated potassium channels. When tested in a model in which dopaminergic (DA) neurons die spontaneously and progressively as a function of time, SP and NKB were all shown to protect and maintain the numbers of tyrosine hydroxylase-labeled neurons in mesencephalic cultures [59].

NEUROTHERAPEUTIC APPLICATIONS OF TK-SYSTEM LIGANDS

As we have outlined in this review, it is clear that the TK receptor-ligand system can have profound effects on multiple neurological disorders, including amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, traumatic brain injury and central motor disorders. The neuroprotective nature of tachykinins makes TK agonists prime candidates for therapeutic agents in neurodegenerative conditions. A vital aspect in the treatment of Parkinson's disease is the prevention of dopaminergic cell death. Multiple TK agonists have been demonstrated to prevent the progressive loss of dopaminergic cells in models of nigrostriatal degeneration [58,59]. With regard to Alzheimer's disease, several studies have indicated an extension of the neuroprotective attributes of SP into the realm of neuronal death induced by amyloid-β (A_β). In the early 1990s, several research teams demonstrated that TK peptide agonists were able to nearly completely reverse the trophic and toxic effects of A_β [126,127].

TK receptor antagonists, specifically TACR1 antagonists, have been especially successful in clinical settings when treating nausea and vomiting [128]. TACR1 antagonists have also demonstrated promise for affective disorders linked with stress and anxiety. Multiple TACR1 antagonists have been shown to attenuate the anxiety-inducing effects of centrally-infused SP agonists [129,130] and later proved to be as effective as paroxetine, a selective serotonin reuptake inhibitor, in treating major depressive disorder in humans [129,131]. There have also been a number of studies investigating the treatment of chemotherapy-induced emesis with MK-869, as well as other TACR1 antagonists. However, MK-869 ameliorates nausea only when taken in tandem with a serotonin 5-HT_3 receptor antagonist and dexamethasone, a known antiemetic [132]. Although research into possible treatment options of TBI using TK receptor antagonists is not as developed as it is in other fields, there are several indicators that point to TACR1 antagonists as a potential therapeutic avenue. TACR1 antagonists have been found to reduce post-ischemic myocardial injury in rats deprived of dietary magnesium, primarily through a potential anti-inflammatory action [133]. Traumatic injury has been shown to produce sustained decline in intracellular magnesium, suggesting that SP may contribute to the detrimental effects of magnesium deficiency [134]. Currently there are two TACR1 antagonists (Aprepipant [129] and Fosaprepipant) marketed for their ability to ameliorate nausea symptomology. However, there are also TACR1, TACR2, and TACR3 antagonists in various phases of clinical trials. Antagonists for the TACR1 are being assessed for addiction/post-traumatic stress disorder (Aprepipant, Vofopitant), major depressive disorder (Orvepitant), seasonal affective disorder (LY-686017, Vestipitant), and schizophrenia (AZD-2624). Antagonists for the TACR2 or TACR3 are also currently under investigation in clinical trials for major depressive disorder (TACR2: Saredutant), acute panic attacks (TACR3: Osanetant), and schizophrenia (TACR3: Talnetant, SSR-241586).

CONCLUSIONS

The extensive involvement of tachykinins (TKs) and their receptors in a wide range of biological functions has made them prime targets for physiological and pharmacological investigation. These peptides seem to display great diversity in their involvement with a number of CNS disorders, ranging from minor roles in ALS and MJD to significant contributions in affective and neurodegenerative disorders. The sheer breadth of the associations between TKs and multiple CNS disorders is likely to lead, via advanced pharmacological targeting [80, 135], to even more TK-based neurotherapeutics. Further investigation of the complex interactions of the TK receptor-ligand system with other neurotransmitter systems will undoubtedly increase the potential impact of novel pharmacotherapeutics targeted towards these TK receptors.

Acknowledgments

This research was supported by the Intramural Research Program of the NIH, National Institute on Aging.

ABBREVIATIONS

AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
CNS	central nervous system
CSF	cerebrospinal fluid
GPCR	G protein-coupled receptor
HD	Huntington's disease
MJD	Machado-Joseph disease
NKA	neurokinin A
NKB	neurokinin B
PD	Parkinson's disease
SP	substance P
TBI	traumatic brain injury
TK	tachykinin

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