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**REVIEW ARTICLE**

# Substance P Regulation in Epilepsy

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**Abstract:** ***Background*:** Epilepsy is a common neurological disease characterized by abnormal temporary discharge of neurons in the central nervous system. In recent years, studies have revealed the localization and changes in the density of neuropeptides, such as substance P (SP) in the pathogenesis of epilepsy. This review is a concise overview of SP and their physiologic and pathologic functions on regulating epilepsy, and the underline mechanisms.

***Methods*:** We research and collect relative online content for reviewing the effects of SP in Epilepsy.

***Results*:** The SP/NK-1 receptor system may induce seizures and play an important role in status epilepticus and in experimental animal models of epilepsy. Newest studies show that several mechanisms may explain the excitatory effects of the SP/NK-1 receptor signaling pathway in epilepsy. By binding to the NK-1 receptor, NK-1 receptor antagonists may block the pathophysiological effects of SP, and further studies are needed to confirm the possible anti-epileptic activity of NK-1 receptor antagonists.

***Conclusion*:** SP plays crucial roles on through binding with NK-1 receptor during epilepsy pathologic processing, and the NK-1 receptor is receiving a great attention as a therapeutic target for treating epilepsy. Thus, the use of NK-1 receptor antagonists for the treatment of epilepsy should be investigated in further studies.

**Keywords:** Neuron, GABA, epilepsy, substance P, Animal, NK-1.

## 1. INTRODUCTION

Epilepsy is a common neurological disease characterized by abnormal temporary discharge of neurons in the central nervous system (CNS). The clinical features of epilepsy are diverse and complex because of the different initiation and transmission pathways involved. The International League Against Epilepsy Commission classifies epilepsy as generalized, focal, or unknown etiology, and the concepts, terminology, and approaches for classifying epilepsy were revised in 2010 [1]. Several reviews have described that in many types of cerebral lesion, including the temporal lobe, frontal lobe, and pallium lesions, are involved in epilepsy [2, 3]. The main type of seizure disorder is temporal lobe epilepsy (TLE), which has been the primary focus of research.

The development of experimental models has provided increasing evidences that during status epilepticus, inhibitory and excitatory mechanisms can lead to continuous seizures. Studies focusing on pathological changes have expanded from macroscopic examination of autopsied tissue to cellular and molecular features. Many studies have also revealed the role of the G-aminobutyric acid (GABA) ergic system in epilepsy, including the location, phosphorylation, and intracellular signaling mediated *via* $GABA_A$ receptors [4, 5]. Furthermore, Jaggi *et al*. [6] suggested that epileptogenic stimuli could enhance the expression of NKCC (sodium potassium chloride co-transporter) which shift GABA mediated hyperpolarization to depolarization, by the accumulation of chloride ions within the neurons, leading to development of seizures. Additionally, electrical coupling mediated by transient receptor potential vanilloid type 1 (TRPV1) cation channels [7] and gap junctions(clusters of intercellular channels) [8] might play an important role in etiology and maintenance of epileptic seizures. Also studies of the hippocampus have revealed the localization and changes in the density of neuropeptides, including neuropeptide Y (NPY), brain-derived neurotrophic factor, ghrelin, somatostatin, and SP in the pathogenesis of epilepsy [9]. Moreover, multiple neuropeptides capable of modulating receptor activity may play diverse roles in epilepsy, by regulating excitatory and inhibitory synaptic transmission [10, 11].

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There has been rapid development in traditional anti-epileptic drugs targeting ion channels and GABA receptors over recent years; however, a large proportion of patients have intractable epilepsy [12]. Liu *et al*. reported that SP receptor NK-1 antagonists could prevent or stop epilepsy associated with SP [13]. Additionally, other researchers have demonstrated that SP receptor antagonists could block the maintenance phase of epilepsy, whereas the traditional anti-convulsant diazepam does not [14, 15].

This review is a concise review of SP and their physiologic and pathologic functions on regulating epilepsy, and the underline mechanisms.

## 2. SP

SP was first isolated in 1931 from the brain and intestine of horses [16]. The amino acid structure of SP, H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-$NH_2$, was reported by Chang *et al*. in 1971 [17]. The structure and physiological function were subsequently determined in more detail, it is one of the most extensively studied active substances [18]. SP is an undecapeptide that belongs to the tachykinin family, the members of which share the same carboxyl terminal. SP differs from the other tachykinins in terms of its pathophysiologic activity and receptor subtypes [19].

SP is ubiquitously expressed in humans and rodents, and it plays many roles in various biological processes. Euler and Gaddum were the first to report the hypotensive and contractile effects of SP on gastrointestinal smooth muscle [16]. Subsequent studies have shown that SP is a neuronal sensory mediator associated with pain transmission because of its high concentration in the dorsal roots of the spinal cord. SP is also associated with growth and development of neuronal tissue [20], inflammation [21], hepatitis [14] and nociception [14, 22]. The pathophysiological effects of SP in the cardiovascular system [23] and CNS, including psychiatric disorders [24] and epilepsy [25, 26] have been reported.

### 2.1. Synthesis of SP

The preprotachykinin-a (PPT-A, TAC1) gene encodes the sequences of SP and neurokinin As (NKAs), including neuropeptide K and neuropeptide-γ [27], whereas neurokinin B (NKB) is derived from the preprotachykinin-b (PPT-B, TAC3) gene, which only encodes its precursor [28]. The PPT-A gene has seven exons and six introns, which can express four different mRNAs (α, β, γ, and δ) *via* alternative transcription. Each mRNA isoform has different exons. The α sequence lacks exon 6, the β sequence includes all seven exons, the γ sequence lacks exon 4, and the δ sequence lacks exons 4 and 6 [29]. The sequence encoding SP is located in exon 3 and the sequence encoding NKA is located in exon 6. Therefore, SP can be encoded from all the mRNA isoforms, and the β and γ mRNAs also encode NKA [30, 31]. Consequently, SP and NKA are often synthesized together and released simultaneously [30]. Moreover, α mRNA is mainly localized in the CNS, whereas the β and γ mRNAs are mainly expressed in the periphery. Following mRNA transcription, translation of SP occurs in ribosomes [32, 33].

### 2.2. Localization of SP in Nervous System

Neural tissues, including neural cells and nerve fibers, are the primary sources of SP, and the syntheses SP is transported to the central and peripheral branches of the primary sensory neurons [34-36]. SP distributed various regions of the CNS, including the rhinencephalon, telencephalon, basal ganglia, ventral pallidum, hippocampus, amygdala, caudate nucleus, septal areas, diencephalon, hypothalamus, mesencephalon, metencephalon, pons, locus coeruleus, substantia nigra, parabranchial nuclei, myelencephalon, and spinal cord [37-39]. Granule cells and interneurons within the hilus, stratum oriens, and stratum radiatum also contain SP [40, 41]. In the hippocampus, SP is primarily expressed in SP-positive cells in the supramammillary nucleus, from extrahippocampal tissue [40]. The expression of SP is high in some cerebral areas, with higher expression in grey matter than in white matter [42]. In addition, the density and distribution of SP expression change markedly with age, peaking between postnatal days 5 and 15 and decreasing thereafter [43, 44].

In the peripheral nervous system, SP immunoreactivity is abundant in the peripheral autonomic ganglia [45], with the highest concentrations in the mesenteric ganglia and celiac ganglia [46].

### 2.3. SP Receptors

Tachykinins modulate biological activities, such as neurotransmitter release and postsynaptic receptor activation, by binding to neurokinin (NK) receptors [47, 48]. NK receptors NK-1, NK-2, and NK-3 are G protein-coupled receptors [49], and each subtype is targeted by specific tachykinins. SP binds to NK-1, NK-2, and NK-3 receptors in its target tissues, but SP preferentially binds to NK-1 receptors [50-52]. Activation of the NK-1 receptor increases intracellular $Ca^{2+}$ concentration, which increases the $Ca^{2+}$ and Cyclic Adenosine monophosphate (cAMP) concentrations, resulting in cAMP response element binding protein and $Ca^{2+}$ increasing gene transcription [53].

The NK-1 receptor consists of seven hydrophobic transmembrane domains, which are connected by extracellular and intracellular loops. There are three extracellular loops (EL1, EL2, and EL3) and a unique amino-tail on the intracellular side, and three loops (C1, C2, and C3) and the conserved carboxyl terminal on the intracellular side. Loop C3 is coupled to the G protein, whereas the second and third transmembrane domains contain the binding sites for agonists and antagonists [54, 55].

The NK-1 receptor gene is a single-copy gene located on human chromosome 2 [56]. Alternative splicing or post-translational modifications yield two isoforms of the NK-1 receptor, derived from differences in the tachykinin receptor 1 gene. The two natural forms differ in the length of their carboxyl-terminal cytoplasmic tails. The full-length receptor consists of 407 amino acids, whereas the truncated receptor, which lacks the intron between exons 4 and 5, consists of 311 amino acids [57, 58].

The two isoforms of the NK-1 receptor exhibit physiological and pharmacological differences. In particular, the

affinity for SP is nearly 10 times higher for the full-length isoform than the truncated isoform [58, 59]. In addition, these isoforms exhibit different receptor kinetics; the long isoform takes 1–2 min to phosphorylate extracellular-regulated protein kinases, whereas phosphorylation does not occur for at least 20 min after exposure to SP in cells expressing truncated NK-1 receptor [60].

In the CNS, the expression of NK-1 receptor is greatest in the caudate-putamen and superior colliculus. It is also expressed at lower levels in the colliculus, olfactory bulb, hypothalamus, hippocampus, substantia nigra, cerebral cortex, septum, striatum, hypothalamus, mesencephalon, and dorsal horn of the spinal cord [37, 61]. In normal neurons, NK-1 receptors are expressed on the plasma membrane of the cell body and dendrites. Binding with SP is followed by rapid internalization of the receptor–ligand complex into the cytoplasm *via* endosomes, and after activating of the intracellular signaling molecules, the internalized receptors are returned to the surface membrane [45, 51].

In addition, several studies have shown that NK-1 receptors may function as autoreceptors, allowing SP to modulate its own release in these cells [62, 63]. Malcangio *et al*. suggested that SP can exert negative feedback on its release by activating inhibitory NK-1 autoreceptors and by blocking $K^+$ channels [62]. *In vivo* [64], exogenous SP exerts inhibitory or excitatory effects on the ganglia, and *in vitro* [65], SP is released from the somata (primary afferent neurons). SP autoreceptors may play important roles in generating and maintaining the release of SP, which might be involved in the pathophysiology of several diseases [66].

## 3. INVOLVEMENT OF THE SP AND NK-1 RECEPTOR SYSTEM IN EPILEPTOGENESIS

The SP/NK-1 receptor system may induce seizures and play an important role in status epilepticus and in experimental animal models of epilepsy [13, 67, 68].

### 3.1. Over Expression of SP in Epilepsy

SP may contribute to the initiation and maintenance phases of self-sustaining status epilepticus. Microinjection of SP into the hippocampus of rats triggered continuous epileptiform activity in response to a proconvulsive stimulus, and the subsequent damage of neurons in this region resembled the pathology of human epilepsy [13]. Similarly, in children with epilepsy, serum and cerebrospinal fluid concentrations of SP were elevated in those with seizure disorders [69].

Many predisposing factors, including kainic acid and perforant path stimulation, induce limbic seizure and status epilepticus in animal models, resulting in changes in SP immunoreactivity in the frontal cortex and hippocampus [70]. The increases in SP expression occur in conjunction with decreases in inhibitory neuropeptide synthesis. Increases in SP expression were mainly observed in the CA3 and CA1 regions of the hippocampus, the dentate gyrus, and mossy fibers exhibiting partially damaged neurons [13].

Indeed, some researchers reported that SP also induced rapid and significant expression of PPT-A mRNA and positive feedback on SP expression to modulate neuron excitability and contribute to the severity of status epilepticus [71-75]. Furthermore, self-sustaining status epilepticus is associated with a specific pattern of hippocampal damage in human epilepsy [13]. In mouse models of epilepsy induced by kainic acid or pentylenetetrazole, knocking out the PPT-A gene attenuated the duration and severity of epilepsy without causing necrosis and apoptosis of hippocampal neurons [76]. These results indicate that PPT-A–null mice lack an active SP/NKA-mediated signaling pathway, which is involved in seizures. Furthermore, a mouse model of neurocysticercosis revealed that seizures could be induced by microinjection of SP into the hippocampus of mice, but not in SP precursor-deficient mice. Pathological examination showed that brain tissue from neurocysticercosis patients expressed SP, whereas tissues from uninfected individuals did not express this peptide [77]. These results suggest that SP and/or NKA are critical factors in the pathophysiology of epilepsy.

### 3.2. SP/NK-1 System may Play an Important Role in Neural Network of Epilepsy

The temporal lobe is one of the most common epileptic foci and TLE often begins in limbic structures, including the hippocampus. Increased NK-1 receptor availability in ipsilateral medial temporal structures is correlated with the frequency of seizures. The SP/NK-1 system may play an important role in this cortical network and may promote excitatory communications between neurons in the TLE. However, other research suggests that remote neurobiological changes are also associated with the occurrence of epilepsy [78-81].

Furthermore, Torsten *et al*. [82] obtained positron emission tomography images of the brain to investigate the neurobiological changes in NK-1 receptor activity in patients with TLE, and they found that the NK-1 receptor activity was significantly increased in both the ipsilateral and contralateral hemispheres in TLE. Additionally, they reported that NK-1 receptor availability may be positively correlated with seizure frequency. Moreover, valproic acid down-regulated the expression of NK-1 receptors in rat and human astrocytes [83].

The supramammillo–hippocampal pathway has a potential role in seizures because it is an efficient excitatory input that terminates in the hippocampus [84, 85]. Pathological analysis of hippocampi obtained from hippocampectomy in patients with intractable epilepsy revealed selective loss of SP-immunoreactive interneurons in the subgranular region of the hilus [86]. In a rat model of epilepsy induced by kainic acid, the number of neurons located in the hippocampal CA1 subregion was reduced compared with the control [87]. In another biopsy study of patients with TLE who underwent hippocampectomy, the number of SP receptor-immunoreactive cells was conserved in the non-sclerotic CA1 region, whereas it decreased in sclerotic cases. This study also revealed reactive changes in SP receptor-positive cells in epilepsy, including intense branching and growth of their dendritic arborization [88].

One report suggested that SP innervation to the hippocampus arises from intrinsic sources (interneurons and granule cells) and extrinsic sources (probably the supramammillary region) [40]. That study also revealed that a large number of mossy axon terminals expressed SP in perforant pathway-stimulated animals. However, other studies found that

SP [37, 41, 89, 90] and PPT-A mRNA [67, 87] were not expressed in principal cells in normal animals, and that the expression of SP in the principal cells of the hippocampus resulted from sustained epilepsy. The immunoreactivity of SP in the mossy fiber terminals, which is derived from excitatory synapses within the pyramidal cells, may support the hypothesis that SP is released by pro-epileptic stimuli; therefore, SP increases synaptic excitability resulting in status epilepticus [13].

In addition, Kim *et al*. [91] demonstrated that nuclei and Purkinje cell in the cerebellar cortex of seizure sensitive (SS) gerbils showed stronger NK-1 receptor immunoreactivity than seizure resistant (SR) gerbils. Author also discussed the possibility that over-expression of NK-1 receptor immunoreactivity may be involved in the excitotoxic insults of Purkinje cells, since SP could augment the expression of the voltage gated $Ca^{2+}$channels (VGCC) which cause Purkinje cell damage. From the above, the SP/NK-1 system may have similar features in epilepsy derived from different brain lesion, although the evidence for this is indirect. More research including animal experiments and clinical results is needed.

### 3.3. Mechanisms of SP/NK-1 Receptor Signaling Pathway in Epilepsy

Several mechanisms may explain the excitatory effects of the SP/NK-1 receptor signaling pathway in epilepsy, including the slow synaptic currents [92], modulating inward rectification [93], and enhanced sensitivity to glutamate [94].

SP, like *N*-methyl-D-aspartate (NMDA), modulates neuronal excitability by changing synaptic currents [92, 95, 96]. It is possible that SP as a neurotransmitter, may prolong the excitatory postsynaptic potentials (EPSP) by further depolarizing the membrane [97], and then removing the voltage-dependent $Mg^{2+}$ blockade of the NMDA receptor ion channel. Binding of SP to the NK-1 receptor could depolarize the membrane by reducing inward rectifying $K^+$ currents [96]. Moreover, an increase in the intracellular $Ca^{2+}$ concentration elicited by SP [93, 98] could promote protein kinase C-dependent phosphorylation of the NMDA receptor [99], and this mechanism might also remove the $Mg^{2+}$ blockade and increase glutamate sensitivity. Glutamate may recruit more NMDA receptors and contribute further to the maintenance phase of self-sustaining status epilepticus. Thus, by modulating neuron excitability *via* inward rectification, SP exerts a self-reinforcing role in self-sustaining status epilepticus.

Another possible factor explaining the mechanism of SP is that, during seizures, the release of glutamate is dramatically increased by SP [13]. Glutamate is an excitatory amino acid that targets quisqualate or kainate receptors, and is a neurotransmitter that modulates EPSP [100]. Overexpression of glutamate often results in status epilepticus and neuronal death [101-103]. In contrast, PPT-A–knockout mice were less vulnerable to kainate-induced status epilepticus and neuronal death [76].

## 4. NK-1 RECEPTOR ANTAGONISTS: A POTENTIAL TARGET FOR TREATING EPILEPSY

According to the previous papers, SP/ NK-1 receptor system is involved in many human pathology (such as depression, cancer, cardiovascular system and pruritus) [14], suggesting that NK-1 receptor antagonists have many promising therapeutic indications. Additionally, NK1 receptor antagonists are safe and well tolerated, and most adverse events are generally mild, such as headache [104]. Now, aprepitant is being put into clinic practice for its antiemetic action [104].

As we know, pathophysiology of epilepsy is associated with activation of the SP/NK-1 signaling pathway [14], and NK-1 receptor antagonists inhibit epileptic seizures [87]. By binding to the NK-1 receptor, NK-1 receptor antagonists may block the pathophysiological effects of SP. Accordingly, these findings suggest that NK-1 receptor antagonists could provide efficient treatments for intractable epilepsy because many patients with refractory epilepsy are resistant to traditional anticonvulsant drugs or do not tolerate the side effects. However, the therapeutic potential of NK-1 receptor antagonists has not been fully explored in animals or humans.

Several agonists and antagonists have been developed and used in studies focusing on the SP/NK-1 signaling pathway. Several studies have also demonstrated the heterogeneity and affinity of NK-1 receptor antagonists, and examined whether selective blockade of the NK-1 receptor can prevent or modify epileptic seizures. NK-1 receptor antagonists can be divided into two groups according to their chemical composition: peptide NK1 receptor antagonists (also called SP antagonists, SP analog antagonists, and SP receptor antagonists) and nonpeptide NK-1 receptor antagonists (including benzyl ether piperidines, perhydroisoindolones, steroids, and tryptophan-based molecules) [105]. Peptide NK-1 receptor antagonists bind to the NK-1 receptor at the extracellular ends of the transmembrane helices, whereas the nonpeptide antagonists bind to deeper regions between the transmembrane segments [106].

The first non-peptide NK-1 receptor antagonist (CP-96,345) was reported in 1991 [107], and since then many more studies have been performed. Although more than 300 NK-1 receptor antagonists have been developed to date, the drugs aprepitant and fosaprepitant, which can cross the blood–brain barrier, are the only NK-1 receptor antagonists available for clinical use [14].

Most research in this field has involved in animal models and the antiepileptic effects of these drugs have been examined alone or in combination with other drugs. It was reported that intranigral injection of NK-1 receptor antagonists alleviated the convulsions induced by maximal electroshocks or intravenous bicuculline in rats [108]. Other NK-1 receptor antagonists, such as spantide II and RP-67,580, prevented or attenuated the convulsions in a rodent epilepsy model associated with seizure-related hippocampal damage [13]. Pretreatment with the NK-1 receptor antagonist CP-122,721-1 decreased seizure activity and it was speculated that this antagonist inhibited kainic acid-induced neuron death in the CA1 subregion [87]. More recently, it was reported that the NK1 receptor antagonist GR205171 (vofopitant) potentiated the anti-epileptic effects of $Na^+$ channel blockers in an animal model. The authors found that vofopitant alone did not have anti-epileptic effects, although it enhanced the anti-

epileptic effects of $Na^+$ channel blockers (including lamotrigine) by blocking NK-1 receptor activity. These results suggest that some antagonists have synergistic effects when used with some ion channel blockers in refractory epilepsy [15]. Peptide antagonists were generally safe and did not have any serious side effects in animal models or clinical trials [109]. Vofopitant did not have CNS side effects at the doses tested, and did not increase the side effects associated with high doses of lamotrigine [15]. One explanation for this is that the antagonists may only act on lesions overexpressing SP or the NK-1 receptor [110].

Despite the abundance of research showing the beneficial effects of NK-1 receptor antagonists in treating epilepsy in animal models, the effects of these antagonists were less favorable in clinical trials. Some investigators attributed this observation to the differences in the amino acid sequence of the NK-1 receptor between species that may alter the antagonists' affinity for the receptor [42, 58]. The lower efficacy of the antagonists was also ascribed to the instability of the structure and their inability to cross the blood–brain barrier in humans. In addition, some peptide antagonists may have neurotoxic effects in the CNS [105]. These factors might also explain why the antagonists have lower affinity than endogenous agonists.

## CONCLUSION

In conclusion, the SP plays crucial roles on through binding with NK-1 receptor during epilepsy pathologic processing, and the NK-1 receptor is receiving a greatest attention as a therapeutic target for treating epilepsy. However, until now the therapeutic potential of NK-1 receptor antagonists on treating epilepsy has not fully been exploited. The use of NK-1 receptor antagonists in intractable cases or in combination with other drugs for the treatment of epilepsy should be investigated in further studies.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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