

Function of Substance P and Substance P Receptor in Exercise

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Abstract—Based on many studies, this paper discusses the relationship between Substance P, Substance P receptor and exercise. There is good evidence to support the role for SP in nociception, inflammation, glandular secretions, and allergic reactions and in the control of gastrointestinal, respiratory and cardiovascular smooth muscle. It elucidates the role of SP and SPR on exercise from the nervous system and muscle. It concludes that comprehensive study on SP and SPR may be the key to sports and sports-related issues.

Index Terms—Function, substance P, substance P receptor, exercise.

I. INTRODUCTION

In 1931, Von Euler and Gaddum demonstrated the presence in the brain and the gut of an unidentified depressor factor that they named substance P (SP) [1]. SP is widely distributed throughout the central and peripheral nervous systems, where they act as neurotransmitters and neuromodulators. Substance P receptor (SPR) (neurokinin-1), one of the three members of the mammalian tachykinin receptor family, acts as the preferential binding site for the undecapeptide SP. SP is reported to be involved in numerous physiological functions. Previous studies suggested that SP and SPR may play an important role in exercise.

II. BIOLOGICAL COMPOSITION AND FUNCTION OF SP

SP is a member of the tachykinin family of molecules, which share a common C-terminal sequence, Phe-X-Gly-Leu-Met-NH₂. The biological composition of SP is NH₃⁺-Arg⁺-Pro-Lys⁺-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂.

There is good evidence to support the role for SP in nociception, inflammation, glandular secretions, and allergic reactions and in the control of gastrointestinal, respiratory and cardiovascular smooth muscle.

Kumar [2] used specific radioimmunoassay's to measure SP, gonadotropin releasing hormone (GnRH) Met-enkephalin in the brain and spinal cord of the domestic pig. This finding is in agreement with the predominant role played by these neural systems in primary afferent mediation of nociceptive impulses. Helme [3] found that neurogenic inflammation induced by the mechanical stimulus of wool

fabric may be mediated by substance P. The neuropeptide substance P is one possible mediator of this interaction, since it can be released into joint tissues from primary sensory nerve fibers. The potential effects of the peptide on rheumatoid synoviocytes were examined. The results show that substance P stimulates prostaglandin E₂ and collagenase release from synoviocytes. Furthermore, synoviocyte proliferation was increased in the presence of the neuropeptide. Similar effects were observed with a truncated form of substance P. Synoviocytes were sensitive to very small doses of the neuropeptide, and its effects were inhibited by a specific antagonist. Thus, the specific stimulation of synoviocytes by the neuropeptide substance P represents a pathway by which the nervous system might be directly involved in the pathogenesis of rheumatoid arthritis. Scott [4] also found that the time course of the response in the inflamed rat knee was related to SP concentration whilst the persistency of the response was positively correlated with the initial level of joint inflammation. Virta [5] suggested that SP play a role in the maturation of the glandular secretory functions using in vitro methods on rat. Rahman [6] experimented on rat and concluded that substance P released from the nasal mucosa through the activation of tachykinin NK1 receptors during the antigen antibody reaction plays an important role in allergic nasal symptoms. Holzer [7] used High performance liquid chromatography to measure concentrations of substance p and neurotensin in the gastrointestinal tract of various mammals and found that SP can control and maintenance gastrointestinal motility. Martini [8] demonstrated that substance P activation of NK1 receptors plays a major role in the modulation of the parasympathetic component of the baroreceptor reflex. SP also has been shown to improve memory and counter age-related performance deficits in animals [9]-[10].

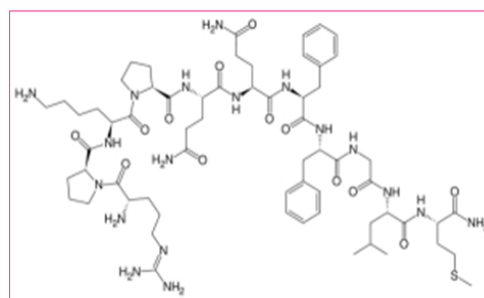


Fig. 1. Structural formula of SP

However, SP is affected by many things. X.D. Yang found that NGF may promote both basal release and capsaicin-evoked release of SP. NGF might increase the sensitivity of nociceptors by increasing the SP mRNA or

Manuscript received October 17, 2012; revised December 4, 2012. This work is contributed equally by Dan Xu and Xiyan Xie as co-first authors.

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VR1 mRNA. RT-PCR were used for detecting the mRNAs of SP and vanillin receptor 1 (VR1) in the DRG neurons. The SP basal and capsaicin (100 nmol/L)-induced release in the culture were measured by radioimmunoassay (RIA). A.M. Skoff [4] found that NGF up-regulation of SP expression requires the involvement of both TrkA and p75, although the specific contribution of each receptor to SP signaling remains to be determined. SP has numerous functions in the body in mammals. We want to know the relation between SP and exercise.

III. BIOLOGICAL COMPOSITION AND FUNCTION OF SPR

SP belongs to the class of small peptides called tachykinins. Tachykinin family is widely distributed in both central nervous system and peripheral tissues, and function as neurotransmitter, neuromodulator, or neurotropic-like factors via mediation of NK-1, NK-2 and NK-3 respectively. NK-1, NK-2, and NK-3 receptors are associated with various biological activities, such as pain transmission, neurogenic inflammation, smooth muscle contraction, and vasodilation. SPR is the natural ligand for the tachykinin receptor NK-1 [11].

SPR are elevated at local sites of inflammation. The biological responses to SP are mediated by NK-1R (SPR). A recent experiment using SPR knockout mice demonstrated that absence of SPR affords protection from immune complex-mediated inflammation in the lung. SPR has been shown to improve memory and counter age-related performance deficits in animals [12]. It works in concert with luteinizing hormone, angiotensin II, and serotonin to modulate their actions. Many of these effects require the selective passage of SP across the blood-brain barrier (BBB) following its release in the periphery. Because SP is a natural ligand for the NK-1 (SPR) receptor and NK-1 (SPR) receptors are widely expressed in neuronal cells and their adjacent tissues, Arvind K investigated the NK-1 receptor play a key role in SP permeation across the BBB [13]. Substance P increases the amount of axon outgrowth from dorsal horn explants cocultured with floor plate explants. Results of experiments with embryonic rats suggest that substance P released from pioneering neuronal pathways may regulate the release of chemo attractants from floor plate cells.

So SPR has important role in body and usually be receptors binding with SP, also, it play a key role in SP transport across the BB.

IV. SP, SPR AND EXERCISE

As is known to all, exercise is carried out by the muscle regulated of the nervous system. The motion signals are transmitted by the nervous system and performed by the muscle. To discuss the relationship between SP, SPR and exercise, we should focus on the nervous system and the muscle.

A. SP, SPR and Nervous System

Substance P (SP) belongs to the class of small peptides called tachykinins that are widely distributed in the central nervous system (CNS) and peripheral nervous system.

Results obtained from Arvind's study demonstrated that the carrier involved in SP permeation across the blood-brain barrier (BBB) is SPR [13]. The transport of SP from the apical side was demonstrated to be via transcytosis. The N-terminal (SP1-4) and C-terminal (SP3-11) fragments were also found to permeate the BBB from the apical side. Morphological studies have revealed the existence of substance P and its high affinity receptor, neurokinin-1 receptor, also called SPR, appeared simultaneously. Mostly, SP should though binding SPR to play its role.

Neurodegenerative disorders usually have dyskinesia. The localization of substance P in brain regions that coordinate stress responses and receive convergent monoaminergic innervation suggested that substance P antagonists might have psychotherapeutic properties. Like clinically used antidepressant and anxiolytic drugs, substance P antagonists suppressed isolation-induced vocalizations in guinea pigs. In a placebo-controlled trial in patients with moderate to severe major depression, robust antidepressant effects of the substance P antagonist MK-869 were consistently observed. In preclinical studies, substance P antagonists did not interact with monoamine systems in the manner seen with established antidepressant drugs. These findings suggest that substance P may play an important role in psychiatric disorders.

SP has been shown to be involved in a variety of neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's [14]. Substance P is released early following acute injury to the CNS as part of a neurogenic inflammatory response. In so doing, it facilitates an increase in the permeability of the blood-brain barrier and the development of vasogenic edema. SP can interact with cholinergic neurons which are sensitive to degeneration in Alzheimer's disease [15]. Endogenous substance P system may play a role in modulating electrical activity of pallidal neurons in Parkinson's disease [16]. Based on the action of Substance P in globus pallidus of parkinsonian rats Qiao-Ling Cui hypothesize that the activity of neurokinin-1 receptors in globus pallidus may be decreased under parkinsonian state. This finding may provide a rationale for further investigations into the potential of pallidal substance P system in the treatment of Parkinson's disease. In Huntington's disease, substance P is depleted in the striatum in parallel with the dorsoventral gradient of neuronal loss [15]. Francesca found the expression of SPR may reflect the fact that striatal SP projection neurons are affected on their enkephalinergic congeners in HD [17].

Moreover, SP is known to produce neurotropic as well as memory-promoting, reinforcing, and anxiolytic-like effects after central or peripheral administration. Previous studies have indicated that intramural injection of substance P or selective neurokinin-1 receptor (SPR) agonist act on nervous system by interact with neurotransmitters. For example, electrophysiological studies revealed that substance P excited nigral dopaminergic neurons [18]. Substance P has also been revealed to promote dopamine release from striatal dopamine terminals [19]-[20], which may be involved in maintaining the integrity of neuronal populations [21].

Besides, substance P could excite GABAergic and dopaminergic neurons in the guinea-pig substantial nigra [22]. L.W. Chen's study has suggested that a sub-population of

striatal GABA-ergic neurons, most possibly GABA-ergic interneurons, may also receive direct physiological modulation by tachykinins through SPR in the basal ganglia of mammals [23]. Immunohistochemical analysis of cultured ganglia indicated that substance P was present in the perikarya of principal sympathetic neurons and in ganglionic nerve processes. Trans synaptic impulses, through the mediation of postsynaptic sodium influx, may decrease substance P in sympathetic neurons.

The role of substance P in Neurodegenerative disorders may be an integration of its effects on multiple neurons in nervous system. Qiao-Ling Cui's [16] studies have indicated that intranigral injection of substance P or selective neurokinin-1 receptor agonist increased striatal dopamine metabolism in Parkinson's disease. At the cellular level, substance P has been shown to directly result in neuronal cell death; functionally, substance P has been implicated in learning and memory, mood and anxiety, stress mechanisms, emotion-processing, migraine, emesis, pain, and seizures, all of which may be adversely affected after brain injury. Inhibition of post-traumatic substance P activity, either by preventing release or by antagonism of the neurokinin-1 receptor, has consistently resulted in a profound decrease in development of edema and marked improvements in functional outcome. This review summarizes the current evidence supporting a role for substance P in acute brain injury.

Also, Nerve growth factor (NGF) increases expression and content of substance P in developing and mature spinal sensory neurons. Anne [24] found that NGF up-regulation of SP expression requires the involvement of both TrkA and p75, and NGF regulates substance P. NGF may promote both basal release and capsaicin-evoked release of SP. NGF might increase the sensitivity of nociceptors by increasing the SP mRNA or VR1 mRNA [25].

B. SP, SPR and Muscle

Many studies show that SP, SPR related. Closely with muscle. Williams' study [26] found that there was a release of irSP from sites in the medulla during the contractions compared to the non-contraction periods. These results provide evidence that SP-like substances may be involved with the central integration of the muscle presser response. Kaufman [27] found that intrathecal injection of the substance P attenuated by more than half the reflex presser response to static contraction of the triceps square muscles of cats. In addition, Nils Lindfors [28] found that a prolonged increase in the extracellular SP-LI concentration was encountered after cervical vagotomy. The results corroborate the suggestion that SP is a mediator of the central response to hypoxia. Low doses of D-Pro2-D-Phe7-D-Trp9-substance P, as specific substance P antagonist, depressed the scratching and biting behaviors elicited by intrathecal injections of substance P, and cutaneous application of algescic substances. Higher antagonist doses caused hind limb paralysis. This suggests that substance P is a neurotransmitter for primary nociceptor afferents and may also have an important function in motor control.

SP can act in muscle and nervous system through binding with its receptor-SPR or other receptors, which can cause

muscle contraction form and EMG changes and change neural signals and neurotransmitters in nervous system. In the study of exercise, we should put SP as factors.

V. CONCLUSION

Substance P is an important neurotransmitter or neuromodulator in central nervous system. Morphological studies have revealed the existence of substance P and its high affinity receptor, neurokinin-1 receptor, in globus pallidus. SP and SPR play both important roles in nerve system and muscle. And exercise is control by nerve system and executed by muscle. So SP and SPR should be the important materials influence exercise. Perhaps, comprehensive study on SP and SPR is the key to sports and sports-related issues. More information and experiments are required to fully understand the functions of SP and SPR and the corresponding mechanisms between SP, SPR and exercise.

ACKNOWLEDGMENT

This research was supported by the Fundamental Research Funds for the Central Universities.

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