



BIOLOGICAL EFFECTS OF SUBSTANCE P IN THE BRAIN

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ABSTRACT

Substance P (SP) is a non-cholinergic neuropeptide produced at different levels in different cell types, including mast cells (MCs) and neurons. SP is involved in the regulation of many central nervous system (CNS) disorders such as anxiety, stress, mood disorders, and neurogenesis, and functions such as synapse growth, dendritic formation, respiration, neurotoxicity, nociception and pain. This neuropeptide produces inflammation after binding to its natural killer (NK) cell receptor. MCs and neurons possess the NK1 receptor and are activated by SP to produce inflammatory molecules such as cytokines and chemokines. In this article, we report that SP not only induces the generation of pro-inflammatory proteins, but also acts synergistically with cytokines such as IL-33 to enhance the inflammatory process.

KEYWORDS: *substance P, brain, CNS, immunology, inflammation*

INTRODUCTION

Substance P (SP) was discovered in 1931 by V. Euler and Gaddum who found that extracts from brain and intestinal tissues had hypotensive and spasmogenic activity. Subsequently, a protein was extracted from these tissues which was called SP. Further studies highlighted that SP is a neuropeptide member of the tachykinin (TAC) family that is present in mammals and distinguished in three subgroups: TAC1, 3, and 4. SP is a non-cholinergic neurotransmitter that is present at different concentrations in different areas of the central nervous system (CNS) (1). For example, SP is found at higher concentrations in the dorsal spinal roots, while it is lower in the ventral roots (2). Levels of SP are elevated in the grey matter, midbrain, postrema area, nuclei, and medullary fibers (3). However, SP concentrations in various brain areas could be species-specific and therefore vary in the various experimental animals used (4).

SP is involved in the regulation of anxiety, stress, mood disorders, neurogenesis, the growth of synapses, dendritic formation, respiration, neurotoxicity, and nociception and pain (5). When SP is injected into the third ventricle in experimental animals, it stimulates respiration and causes a slight increase in blood pressure (6).

DISCUSSION

Substance P (SP) in inflammation

SP is a protein made up of 11 amino acids that is produced by several cell types, including neurons and immune cells (7). SP acts by binding to its G protein-coupled neurokinin receptors (NKR), which include NK1R, NK2R, and NK3R (8). From these receptors, NK1R appears to have greater affinity for SP. SP binds the NK1R receptor in immune cells,

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causing an immune response, including the reaction towards microbes (9). In addition, SP has been observed to mediate tissue homeostasis and wound healing (9).

SP can mediate neurogenic inflammation and can be released after stimulation of the sensory nerves (10,11). This neuropeptide is biologically active in endothelial cells and smooth muscle cells and increases vascular permeability with the consequent leakage of plasma and the formation of edema (12,13). SP also activates intracellular adhesion molecules (ICAMs) as well as vascular cell adhesion molecules (VCAMs) in vascular epithelial cells (14,15). Mast cells (MCs) treated *in vitro* with SP generate more VEGF than untreated samples (16,17). The action of SP on the vessels causes an increase in vascularization with inflammatory cells crossing the tissues (18,19). SP works by binding to its NK1 receptor and mediates itching, which can be inhibited by antagonist drugs that block NK1 (20,21) (Fig.1).

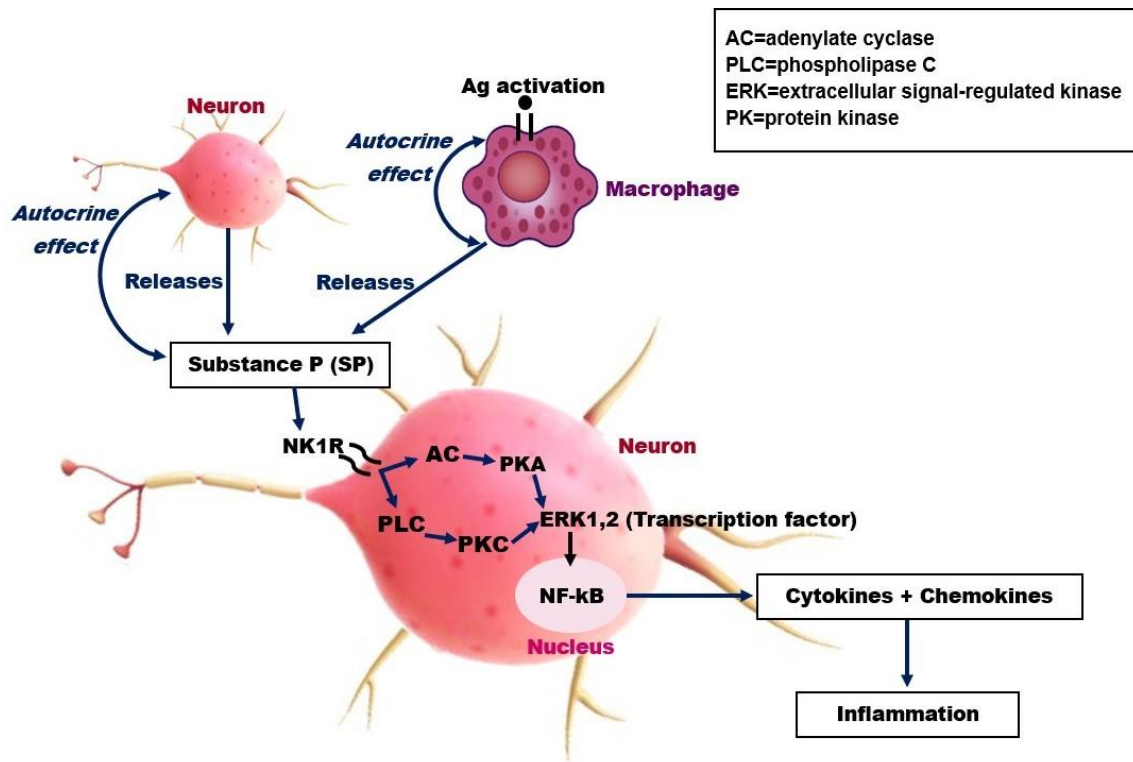


Fig. 1. A schematic reproduction depicting Substance P (SP) secretion by neurons and macrophages.

Substance P and mast cells (MCs)

MCs are immune cells derived from bone marrow that migrate and mature in tissues throughout the human body, which mediate innate and adaptive immunity (22,23). In addition to expressing the FcεRI receptor, MCs show other ligands on their surface, including those of neuropeptides such as SP (24,25).

It has been reported that IL-33 significantly increases the ability of SP to stimulate MCs to secrete VEGF, tumor necrosis factor (TNF), and IL-1 β , selectively without tryptase granule release (26,27). In their interesting article, Theoharides et al. provide much information on SP-mediated inflammation in relation to IL-33 (26).

In an *in vitro* study, the treatment of a line of MCs (LAD2) with SP plus the cytokine IL-33 achieved a synergistic effect on the stimulation of the potent pro-inflammatory cytokine IL-1 β , compared to the administration of cells treated with IL-33 alone (28). These results demonstrate that SP is not only a potent pro-inflammatory molecule, but that it is also able to synergistically enhance other inflammatory cytokines such as IL-33 (29,30). In addition, the authors reported that SP alone has a stimulatory effect on IL-1 β production in MCs only at high concentrations (1 μ M), while at lower concentrations (0.01–0.1 μ M) there was no effect. These effects were also confirmed by IL-1 β gene expression which demonstrated an active participation of SP in inflammatory effects induced by IL-1 β . However, these reactions did not affect the inflammasome protein (NLRP3 or ASC) levels. Blocking the NK1 receptor on MCs suppressed the secretion of IL-1 β . In this study, it was evident that SP and its receptor NK1 were involved in the induction of IL-1 β . The authors concluded that in combination with IL-33, SP synergistically induces IL-1 β secretion from MCs.

CONCLUSIONS

In conclusion, SP that is produced by different cells, including neurons and MCs, induces cytokines and chemokines that mediate many neurological disorders. In addition, by binding its receptor NK1, SP can act synergistically with certain cytokines, such as IL-33, and induce inflammation.

Conflict of interest

The author declares that they have no conflict of interest.

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