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Secretoneurin and neurogenic inflammation[1]

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ABSTRACT

AIM: Review of evidence that the 33-amino-acid polypeptide secretoneurin, which is generated by proteolytic cleavage of secretogranin Ⅱ, plays a role in neurogenic inflammation. **METHODS**: Survey of the literature using a MEDLINE search database. **RESULTS**: Secretoneurin is synthesized in spinal ganglia, transported through the dorsal roots and stored in the axon terminals of primary afferent neurons. Investigations using capsaicin suggest that secretoneurin functions as an excitatory transmitter. Secretoneurin specifically activates various cell functions including the chemotactic migration of monocytes, eosinophils, fibroblasts, smooth muscle cells, and endothelial cells, which suggests that the peptide may modulate inflammatory reactions. Secretoneurin receptors have been functionally characterized. They are G-proteins linked and effects are abrogated by inhibition of protein kinase C. **CONCLUSION**: With actions as diverse as those seen with other mediators such as tachykinins, secretoneurin may be considered another sensory neuropeptide with modulatory potential in neurogenic inflammation.

INTRODUCTION

Capsaicin, the main pungent ingredient in "hot" chili peppers, elicits burning pain by activating specific (vanilloid) receptors on unmyelinated sensory nerve endings[1]. Sensory nerves have an efferent function in addition to their afferent function of conducting chemoreceptive impulses to the brain. Chemical irritants that activate sensory nerves cause plasma leakage in the skin, respiratory tract, and other organs by triggering the release of substances from sensory nerve fibers, which is a characteristic of neurogenic inflammation. Substance P, which is synthesized and released by some sensory neurons, appears to be the main active mediator[2], although other tachykinins, calcitonin gene-related peptide, and other peptides may also participate. Substance P is the primary mediator responsible for plasma leakage, acting via tachykinin NK-1 receptors, whereas both calcitonin gene-related peptide and substance P induce vasodilatation. Expression of neuropeptides is up-regulated in sensory neurons following inflammation[3,4].

Neurogenic inflammation results from the action of neuropeptides on their specific receptors. The receptors involved in plasma leakage are located on the endothelial cells of postcapillary venules and collecting venules. Plasma leakage is transient, however, the magnitude of the response can increase in pathological conditions such as infection, allergen exposure, inhalation of cigarette smoke, and other irritants, which results in a chronic inflammatory condition characterized by activation of various other cells types[5].

Inducible nitric oxide synthase-derived nitric oxide is capable of potentiating neurogenic plasma leakage in airways[6]. Tachykinins are normally degraded and inactivated by neutral endopeptidase, and vascular effects of tachykinins are augmented in neutral endopeptidase knock out mice[7]. A variety of factors

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is able to reduce neutral endopeptidase activity, thus enhancing the effects of the peptides[8]. Calcitonin gene-related peptide has protector properties but its ability to limit the extent of inflammation is strongly impaired in inflammatory conditions[9]. Sensory neuropeptides regulate the release of cytokines and chemokines, which are important in the pathophysiology of various inflammatory diseases[10]. Under certain conditions and in correlation with clinical events, levels of the neuropeptides can become elevated in patient plasma or tissue fluids[11].

The formation of intrapulmonary immune complexes in mice generates a vigorous inflammatory response characterized by microvascular permeability and polymorphonuclear neutrophil influx. In a study by Bozic *et al*, gene-targeted disruption of the tachykinin NK-1 receptor protected the lung from immune complex injury, as did disruption of the C5a anaphylatoxin receptor; immunoreactive substance P was measurable in fluids lining the lung at time points before neutrophil influx and may thus be involved in an early step in the inflammatory response[12]. The neurogenic component of the cellular inflammatory response to interleukin-1 is significantly altered in tachykinin NK1 receptor knockout mice[13].

Neuropeptide receptors on cells of the inflammatory site play an important role in the development of neurogenic responses. Effects on the migratory behaviour of leukocytes and other cells appear to be play a particular role in neurogenic inflammation.

The release of neuropeptides at the local site and receptor-mediated activation of inflammatory cells have been suggested to form a biochemical basis of neuroimmune interactions[14].

SECRETONEURIN AS A SENSORY NEUROPEPTIDE

Secretogranin Ⅱ is an acidic secretory protein of endocrine, neuroendocrine and neuronal tissues. It comprises, together with chromogranins A and B, the class of proteins collectively called chromogranins. Secretogranin Ⅱ is the precursor of a recently discovered neuropeptide[15]. Using antisera in rabbits to conjugates of two synthetic peptides (bovine secretogranin 133 – 151 and rat secretogranin 154 – 186) flanked in the primary structure of secretogranin Ⅱ by pairs of basic residues the proteolytic processing of this protein was investigated[16]. The highest degree of processing of secretogranin Ⅱ (>90 %) occurred in brain. One of the peptides (secretogranin 133 – 151) did not appear to be generated to any significant extent. The other peptide, secretogranin 154 – 186, however, was formed *in vivo*, and in brain the free peptide represented the predominant form. The detected concentrations were comparable to those of established neuropeptides. In order to indicate the special relevance of secretogranin Ⅱ and of this peptide for brain it was named *secretoneurin*[16].

In the rat spinal cord and lower brainstem, a high density of secretoneurin fibers and terminals was found. The highest number of secretogranin Ⅱ messenger RNA-containing cells was found in lamina Ⅱ of the dorsal horn and in neurons of the dorsal root ganglia. The distributions of secretoneurin and substance P were strikingly similar. Calcitonin gene-related peptide and secretoneurin overlapped in the outer laminae of the dorsal horn, in the lateral cell column, and probably in some motoneurons. Like substance P and calcitonin gene-related peptide, secretoneurin is a peptide highly concentrated in the terminal field of primary afferents and in sympathetic and parasympathetic areas[17].

In the human spinal cord, the density of secretoneurin-like immunoreactivity was high in the superficial dorsal horn and in the lateral column of autonomic arcs. The ventral horn displayed low to moderate density of secretoneurin-like immunoreactivity and prominently outlined motoneurons[18]. The congruent distribution of secretoneurin and substance P to the termination of primary afferents may indicate that secretoneurin is involved in modulation of pain.

The localization of secretoneurin in the dorsal horn of the spinal cord suggested its release from primary afferent neurons. In a study by Kirchmair *et al*[19], normal rats and rats pretreated neonatally with capsaicin to destroy selectively polymodal nociceptive fibres were used. Capsaicin treatment led to a marked depletion of secretoneurin in the substantia gelatinosa, but not in other immunopositive areas of the spinal cord and to a substantial loss of small secretogranin Ⅱ messenger RNA-containing dorsal root ganglia neurons. Radioimmunoassay revealed a decrease of secretoneurin in the dorsal spinal cord, the trachea, heart, and urinary bladder of capsaicin-treated rats, demonstrating

that secretoneurin is a neuropeptide which is stored in and released from capsaicin-sensitive, primary afferent neurons[19].

In dental pulp secretoneurin localized in varicose nerve fibres that were frequently associated with blood vessels and no significant correlation was found between the immunoreactive levels of secretoneurin and calcitonin-gene related peptide[20]. Studies demonstrate that chromogranins A and B, and secretoneurin are transported with fast axonal transport in the peripheral nerves, and that they are differentially distributed in different types of neurons in the peripheral nervous system and the spinal cord, suggesting that each of them may play a special role in subsets of neurons[21,22].

SECRETONEURIN EFFECTS ON INFLAMMATORY CELLS

Leukocytes. Secretoneurin triggers the selective migration of human monocytes *in vitro* and *in vivo*, and combinations of secretoneurin with the sensory neuropeptides, substance P, or somatostatin, synergistically stimulate such migration[23]. The attraction of monocytes represents the first established function of secretoneurin as a sensory neuropeptide. A significant migratory response of the monocytic cell line U937 to secretoneurin or a C-terminal fragment of secretoneurin at concentrations in the nanomolar range was seen in transendothelial migration models as well[24]. Migration was comparable to a maximal effect induced by the monocyte chemotactic agent *N*-formyl-Met-Leu-Phe, and rabbit anti-secretoneurin antibodies were able to specifically block the neuropeptide effect[24].

Secretoneurin acts as an eosinophil chemoattractant comparable in its potency to interleukin-8, and checkerboard analysis, usage of a specific anti-secretoneurin-antibody, and receptor desensitization experiments confirmed the chemotactic activity[25].

Whether phagocytes other than monocytes and eosinophils are targets of secretoneurin action is currently unknown. Since previous data suggest that secretoneurin does not induce chemotaxis of neutrophils at relevant concentrations[23], neutrophil priming for respiratory burst activity, adherence to endothelial cell monolayers and effects on chemoattractant-stimulated migration of neutrophils was investigated. Priming of neutrophils with secretoneurin failed to enhance triggered respiratory burst activity or adherence to endothelial cells as compared with tumor necrosis factor-alpha, a well-known neutrophil-priming cytokine; pretreatment of neutrophils, however, revealed an increase in spontaneous locomotion, and significant antagonism of formylpeptide-stimulated migration[26]. Therefore, neutrophils appear to be specifically affected by secretoneurin possibly by activation of a priming-type receptor.

Secretoneurin, known to induce monocyte chemotaxis, was unable to affect lymphocyte migration or proliferation *in vitro*[27].

Mesenchymal cells. Secretoneurin triggers the selective migration of human skin fibroblasts *in vitro*, but does not stimulate their proliferation; the attraction of human skin fibroblasts is mediated by the C-terminal fragment of the peptide[28] as was observed for monocytes and eosinophils[23,25]. Secretoneurin also stimulates specific migration of cultured arterial smooth muscle cells from rat thoracic aorta, and initiates DNA synthesis and cell proliferation[29]. In endothelial cells, secretoneurin induces migration but inhibits proliferation[30]. Activation of endothelial cells by secretoneurin induced in endothelium increased adhesiveness to neutrophils[31].

SECRETONEURIN SIGNALING IN INFLAMMATORY CELLS

Preincubation of monocytes with pertussis toxin inhibited secretoneurin chemotaxis; staurosporine, an inhibitor of protein kinase C, significantly decreased secretoneurin-induced chemotaxis of monocytes, suggesting that protein kinase C may be involved in the signaling, and tyrphostin-23, which inhibits tyrosin kinase, did not affect secretoneurin-induced chemotaxis of monocytes. The data suggest that secretoneurin uses a signaling mechanism in monocytes that is coupled to pertussis toxin-sensitive G proteins. Involvement of phospholipase C beta as a result of protein kinase C activation was suggested by a secretoneurin-induced increase of intracellular Ca^{2+} concentration in monocytes[32].

Preincubation of eosinophils with effective concentrations of staurosporine or tyrphostin-23 showed no effect, whereas treatment with wortmannin or 3-

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isobutyl-1-methylxantin completely blocked secretoneurin-induced migration, demonstrating that secretoneurin-stimulated human eosinophil chemotaxis is mediated via a unique and specific signal transduction pathway that involves activation of phosphodiesterases and wortmannin-sensitive enzymes, ie, phospholipase D and phosphatidylinositol-3-kinase[25,33].

Secretoneurin induced in endothelium an increase in adhesiveness to neutrophils in a protein kinase C-dependent manner[31].

SECRETONEURIN RECEPTORS OF MONOCYTES

Specific binding sites for $^{[125]}$I-BH-secretoneurin were identified on human Mono Mac 6 cells, a monocytic cell line. Scatchard analysis revealed a single class of binding sites with a K_d value of 7.3 nanomolar and a B_{max} of 322 femtomol/milligram protein. Competition studies demonstrated that the 15 C-terminal amino acids of secretoneurin could displace authentic secretoneurin, whereas shorter fragments were inactive. Other sensory neuropeptides like substance P, calcitonin gene-related peptide, or galanin as well as the chemokine receptor ligand RANTES or the typical chemoattractant *N*-formyl-Met-Leu-Phe could not displace secretoneurin[34]. In another study[35] the chemoattractants monocyte chemotactic protein-1, monocyte chemotactic protein-2, or *N*-formyl-Met-Leu-Phe could not compete for secretoneurin binding sites confirming that secretoneurin may bind to a novel chemotactic receptor. Additional studies by Kong *et al*[35] showed that neither secretoneurin nor monocyte chemotactic protein-2 induced a rise in cytosolic Ca^{2+}, and chemotaxis to secretoneurin was inhibited by cholera toxin and pertussis toxin; chemotactic desensitization studies demonstrated that chemoattractant *N*-formyl-Met-Leu-Phe, monocyte chemotactic protein-1, monocyte chemotactic protein-2, and secretoneurin, could all desensitize monocytes to subsequent secretoneurin stimulation. Thus in two independently performed studies, a functional monocyte cell surface receptor for secretoneurin was characterized.

CONCLUDING REMARKS

Leukocytes and mesenchymal cells are called upon when tissue sustains an immunological, mechanical or chemical injury. The cells migrate into the site of inflammation, release mediators, proliferate, and synthesize and remodel matrix. These cellular responses are in part mediated locally by the release of neuropeptides from sensory nerve endings. Experimental evidence suggests that secretoneurin is capable to specifically affect various functional aspects of leukocytes, fibroblasts, and vascular wall cells.

There is only limited data confirming these novel pathophysiological mechanisms *in vivo*. First experimental support for a potential pathophysiological relevance of the chemotactic potential of secretoneurin comes from Storch *et al*[36] who tested whether the local presence of secretoneurin within the central nervous system of the rat may influence the topographical distribution of inflammatory infiltrates in acute T-cell mediated encephalomyelitis. A clustering of macrophages, but not of T-lymphocytes, was seen at sites of secretoneurin immunoreactivity in all stages of experimental autoimmune encephalomyelitis which is in line with the chemotactic potency of the neuropeptide[23,24,27,32,35]. Data also indicate for the first time that local neuropeptides may play a role in leucocyte recruitment into inflammatory lesions of the central nervous system.

Immunocytochemistry provided evidence for the presence of sub-intimal secretoneurin-immunoreactive nerve fibres in knee synovium in osteoarthritis and few immunoreactive fibres in rheumatoid arthritis these being mostly localized in deep stroma. Secretoneurin is also detected in normal and osteoarthritic synovial fluid and levels are down-regulated in rheumatoid joint[37]. It is currently unknown whether secretoneurin in fact has a role to play in rheumatic diseases as compared with other sensory neuropeptides.

Since secretoneurin is present in lung and bronchial tissues, its effect on eosinophil migration[25] may be of particular importance for eosinophil-mediated pathophysiological events. Secretoneurin is expressed in extrinsic primary afferent nerve fibres and intrinsic enteric neurons of the gut as well as neuroendocrine cells. Even though most of the functional evidence for secretoneurin actions in the gastrointestinal tract is still lacking, its abundant presence in neurons, nerve fibers and neuroendocrine cells together with known functions on inflammatory cells suggest a role of secretoneurin in

bowel inflammation.

The origin of chromogranins lies in a gene that arose many millions of years ago and secretoneurin has been isolated from a diverse array of species from vertebrate classes and invertebrate phyla [15]. Essentially all of the recently discovered putative central nervous system peptides are measurable in human cerebrospinal fluid as is secretoneurin [15]. There is evidence that secretoneurin is synthesized in spinal ganglia, transported through the dorsal roots and stored in the axon terminals of primary afferent neurons [19,21,22]. These and other results suggest that secretoneurin functions as an excitatory transmitter of the primary afferent fibers. Investigations using the compound capsaicin are consistent with the hypothesis that secretoneurin may be an important neurochemical mediator of certain kinds of noxious peripheral stimuli [19]. Elaboration of the roles of secretoneurin as novel sensory neuropeptide will no doubt shed light on many disease states in which there seems to be sensory neuron involvement.

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Secretoneurin 和神经原性炎症

关键词 secretoneurin; 神经肽类; secretogranin Ⅱ; 嗜铬粒蛋白; 免疫系统; 白细胞; 成纤维细胞; 内皮; 信号肽类; 神经原性炎症

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