A Peptide from the Submandibular Glands Modulates Inflammatory Responses

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Key Words

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Abstract

Background: The cervical sympathetic trunk-submandibular gland (CST-SMG) axis plays an important role in inflammation. An immunoregulatory heptapeptide, submandibular gland peptide T (SGP-T), was isolated from submandibular glands, and several of its biological activities have been identified. **Results:** SGP-T reduced shock-induced hypotension and allergen-induced disruption of migrating myoelectric complexes and the magnitude of smooth muscle contraction. The heptapeptide inhibited the influx of neutrophils into carrageenin-soaked sponges. **Conclusion:** SGP-T has several biological activities that collectively help explain the ability of the CST-SMG axis to regulate inflammation.

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Introduction

Despite an early review by Barka [1] identifying the submandibular glands as an important glandular system involved in the regulation of growth, differentiation and homeostasis, these glands are still viewed as an accessory digestive structure that is one of the principal sources of digestive enzymes. However, studies carried out over the last few decades have firmly established an essential role for these glands in systemic tissue repair and in the regulation of immune system function [2]. These immunomodulating functions of the submandibular gland are under the control of the nervous system in what is considered a neuroendocrine unit, the cervical sympathetic trunk-submandibular gland (CST-SMG) axis [3].

Perturbation of this axis by performing a cervical sympathetic denervation results in attenuated late-phase pulmonary inflammation induced by systemic anaphylaxis [4] and produces an enhanced hypotensive response to intravenously administered endotoxin [5]. Since this aggravated

hypotensive response to endotoxin was also seen in rats with their submandibular glands removed [5], we postulated the presence of submandibular gland factors whose release from the glands attenuates the cardiovascular and immunological effects of endotoxin. A heptapeptide, submandibular gland peptide T (SGP-T), was subsequently isolated from rat submandibular

glands with antiendotoxic shock activity. This report describes several biological activities of SGP-T.

Results

Synthetic SGP-T was dissolved in 0.9% NaCl and administered, by injection into the penile vein, to halothane-anesthetized rats that were prepared for one of several different in vivo assays:

(1) SGP-T, at a dose as low as 1 µg/kg given 90 min prior to administration of lipopolysaccharide (*Salmonella typhosa*; 3.5 mg/kg), decreased by 50% the toxin-induced de-

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crease in mean arterial blood pressure in sialadenectomized Sprague-Dawley rats. A substantially higher dose (100 µg/kg) was needed to reduce to a similar extent the hypotensive effects of endotoxin in rats with intact submandibular glands.

At doses of 35 and 100 µg/kg, administered 10 min prior to challenge with antigen, SGP-T reduced by 75% the anaphylactic hypotension in nematode (*Nippostrongylus brasiliensis*) or egg-albumin-sensitized Sprague-Dawley rats.

In another model of anaphylaxis, the disruption of migrating myoelectric complexes of the intestine, induced by duodenal instillation of antigen into egg-albumin sensitized Hooded-Lister rats, was monitored. SGP-T (100 µg/kg), injected intravenously 10 min before challenge, totally blocked the antigen-induced perturbations of gastrointestinal motility. Interestingly, strain differences were detected in the ability of SGP-T to reduce intestinal anaphylaxis in isolated organ baths. At concentrations of 0.5 µM, SGP-T did not alter antigen-induced contractions of jejunal smooth muscle obtained from ovalbumin-sensitized Hooded-Lister rats, whereas this same dose of peptide reduced ovalbumin-induced contractions of the jejunal segments obtained from sensitized Sprague-Dawley rats by 50%.

To examine the effects of SGP-T on neutrophil chemotaxis, carrageenin-soaked sponges were implanted sub-cutaneously in the scapular region of Sprague-Dawley rats, and the number of neutrophils migrating into the sponges were counted 24 h later. Intravenous SGP-T at doses of 35 and 100 µg/kg, administered at the same time the sponges were implanted, reduced neutrophil influx into the carrageenin-soaked sponges by 50%.

Discussion

This report describes some biological activities of a small peptide that is probably generated from a prohormone, the SMR1 protein, which is found in the submandibular glands of male rats [6]. The sequence of SGP-T is located near the COOH terminus of the 146-amino acid SMR1 protein, which is synthesized by the VCS- α 1 gene [7]. The diverse profile of biological activities of SGP-T indicates that this peptide alters the actions of immune and vascular cells such as mast cells (anaphylactic reactions), neutrophils (chemotaxis, endotoxemia) and possibly macrophages, platelets and endothelial cells (endotoxemia). Consequently, a major question that needs to be resolved, and that is presently being investigated, concerns the mechanism of action of the peptide.

The identification of SGP-T supports our earlier suggestion that the CST-SMG axis is an important neuroendocrine structure involved in the regulation of immune and cardiovascular

responses to inflammatory stimuli [2, 3]. Furthermore, within the context of neuroimmunology, SGP-T may be a valuable tool for investigating the regulation of the synthesis and release of a submandibular gland peptide in relation to the modulation of inflammatory reactions.

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