Biomedical Research 2003; 14 (1): 30-37
Special issue: Autonomic Nervous System
Dedicated to Professor Geoffrey Burnstock

The cervical sympathetic trunk – submandibular gland neuroendocrine axis: Its role in immune regulation

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Introduction

The submandibular glands contain and secrete a large number of physiologically active proteins and peptides such as digestive enzymes, growth factors, homeostatic proteases and regulatory proteins and peptide hormones [1, 2]. These molecules subserve a range of biological functions essential for the maintenance of the health and the functioning of the oral cavity and the digestive tract [1, 3-6]. However, they also participate in physiological adjustments related to the maintenance of systemic immunological and physiological homeostasis [7,8]. For example an endocrine function for nerve growth factor (NGF) released from salivary glands was established in the 1970's [9]. Subsequently, a significant relationship between the endocrine function of the salivary glands and social behaviour in mice was described [10,11] suggesting a potential role for the autonomic nervous system in regulating release of NGF.

Immunomodulatory influences exerted by salivary glands, which include the healing of oral peripheral and internal wounds [5,12]) and the regulation of systemic inflammatory reactions [13-16] have been described. Where studied all the regulatory functions of the salivary glands have been shown to be under central nervous system control and mediated by both the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS). It was, therefore, highly probable that the immunoregulatory function of the salivary glands would likewise be under ANS control. This appears to be the case. The parasympathetic nerves stimulate the secretion of saliva containing small quantities of biologically active peptides with putative immunoregulatory functions [1]. β-adrenergic stimulation also increases the synthesis and release of these same peptides. However, α-adrenergic stimulation stimulates the secretion of growth factors and homeostatic proteases from cells into the blood and causes secretion of large amounts of kallikrein, NGF, epidermal growth factor (EGF) and renin into the saliva to a greater extent than β stimulation [17-20]. Direct stimulation of sympathetic nerves releases kallikrein into the saliva and blood [1]). Sympathetic nerves also regulate gene expression for NGF and EGF [21].

In the past twelve years considerable data have accumulated supporting the concept of a cervical sympathetic trunk— submandibular gland (CST-SMG), neuroendocrine regulatory axis that modifies inflammatory responses [7,22,23]. Following the defining of this physiological regulatory system two novel peptides were isolated from the submandibular glands of rats which exert anti-inflammatory actions and which appear to be the endocrine mediators of this novel immunoregulatory system [15]. In the following sections we will first summarize the key evidence leading to the discovery of the CST-SMG axis then describe the isolation and identification of the putative SMG regulatory peptides. Finally, we will briefly discuss the physiological and immunomodulatory properties and the putative mechanism(s) of action of one of these peptides, submandibular gland peptide T (SGP-T).

The Cervical Sympathetic Trunk Submandibular Gland Axis

Preganglionic axons project from the upper thoracic segments down the cervical sympathetic trunk, to synapse on postganglionic neurons in the inferior and superior cervical ganglia. The postganglionic neurons of the superior cervical ganglion (SCG) innervate the upper thorax, neck, skull and facial structures 24]. The endocrine organs located in these areas include the pineal, thyroid, parathyroid and salivary glands, suggesting a significant role for the SCG within the neuroendocrine system. Unilateral SCG ganglionectomy (SCGx) enhances contact hypersensitivity and delayed type reactions in the submandibular lymph nodes of mice [25] indicating a direct effect of the sympathetic innervation on the murine immune system.

In rats sensitized by infection with the nematode worm, *Nippostrongylus brasiliensis* (Nb), intravenous challenges with the sensitizing Nb surface antigen leads to a pronounced influx of neutrophils and macrophages into the brocho-alveolar spaces. This is markedly attenuated by SCGx and SCG decentralization (i.e. cutting the connection between the inferior and superior cervical ganglia,

thereby severing the preganglionic input to the SCG) [26]. These procedures also decrease the phagocytotic ability and respiratory burst of peripheral blood neutrophils [27] and depress the neutrophil chemotaxis to N-formyl-methionyl-leucyl=phenylalanine and TNF production by alveolar macrophages [28]. Bilateral removal of the SMGs was without direct effect but abolished the consequences of SCGx and decentralization. These observations were explained by the hypothesis that the sympathetic nerves inhibit the release of a putative anti-inflammatory mediator from the SMGs.

In contrast, the hypotensive effects of endotoxin (LPS) were increased following all these surgical interventions suggesting that in this experimental model the sympathetic nervous system stimulates the release of an anti-shock factor [13]. These results are summarized in Figure 1. These results appear contradictory though they might be explained by the fact that different challenges release different mediators that are differentially regulated by the sympathetic nervous system.

However, as will be discussed in later sections, the SMG contains a novel heptapeptide that down-regulates both LPS and anaphylaxis-induced reactions suggesting a common mediator. Moreover, while there is abundant evidence for sympathetic and adrenergic stimulation of salivary exocrine and endocrine secretions there are no reports of direct sympathetic or adrenergic inhibitory regulation of salivary secretions. Therefore, another explanation for this apparent anomaly is required.

The anaphylaxis experiments studied a late phase infiltration of the lung by leucocytes following a period of hypotension. This hypotension would have been compensated for by sympathetic-mediated vasoconstriction and reduction of blood flow to the SMG. As discussed later, one of the putative anti-inflammatory mediators is of acinar cell origin. It has been shown that salivary exocrine secretion is suppressed or totally blocked when severed sympathetic nerves are electrically stimulated at a frequency that reduces blood flow below basal levels [29]. However, if the severed nerves are stimulated at a lower frequency that restores blood flow to basal rather than below basal levels, a sustained secretion of saliva is produced demonstrating the existence of sympathetic secretomotor innervation to the SMG [30]. Hence activation of sympathetic vasomotor nerves will inhibit gland secretion by reducing blood flow whereas the sympathetic secretomotor nerves will directly stimulate secretion. This provides a satisfactory explanation of the apparent anomaly of differential regulation by the CST-SMG axis of early endotoxic and late phase anaphylactic reactions

Isolation and Identification of the putative SMG anti-inflammatory mediators

These earlier studies suggested that the CST-SMG immune regulatory system depends on the sympathetic regulation of the release of anti-inflammatory mediator(s) that would reduce the severity of endotoxic or anaphylactic reactions. Since then there has been independent confirmation of the role of the SMGs in endotoxin-induced inflammation [31]. In order to determine the SMG-derived factors responsible for the modulation of these reactions, studies were carried out using classical peptide isolation techniques. First, it was established that crude extracts of submandibular glands would reverse the enhanced LPS-induced hypotension following extirpation of the SMG [15]. Subsequently, these extracts were subjected to molecular weight cut-off filtration followed by preparative, reverse phase, high performance liquid chromatography (HPLC) and finally analytical HPLC purification. At each stage of this process, isolated fractions were tested in the same manner as the crude extract and those that reversed the LPS-induced hypotension proceeded to the next step of the purification process. As a result, two novel peptides were isolated: the pentapeptide, submandibular gland

Table I: Novel SMG anti-inflammatory peptides: Definitions and Sequences

Peptide Name	Acronym	Sequence	Letter code
Submandibular gland peptide S	SGP-S	Ser-Gly-Glu-Gly-Val	SGEGV
Submandibular gland peptide T	SGP-T	Thr-Asp-Ileu-Phe-Glu-Gly-Gly	TDIFEGG
FEG*	Big FEG	Phe-Glu-Gly	FEG*
feG*	Little FEG	phe-glu-Gly	feG*

**Capital letters denote L-isomeric forms and small letters D-isomeric forms of amino acids*

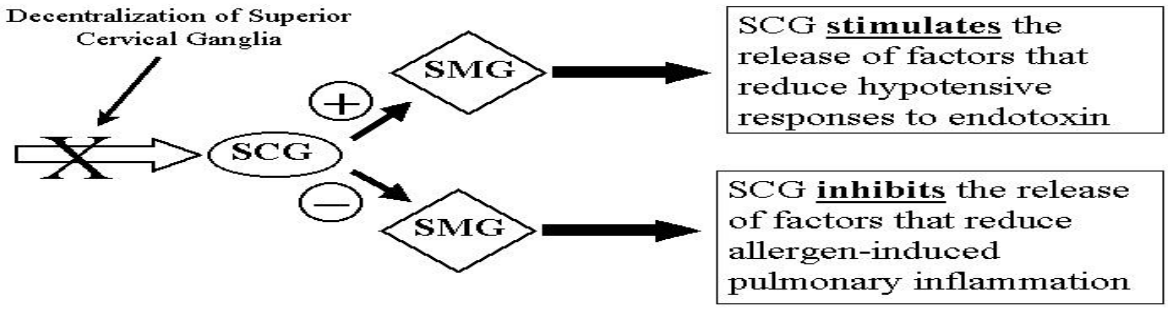

Figure 1: Immunomodulatory actions of the cervical sympathetic trunk-submandibular gland axis

Fig. 1: *Contrasting effects of the cervical sympathetic trunk-submandibular gland axis in modulating endotoxin- and allergen-induced inflammations. Sympathetic denervation of the submandibular glands by removal of the superior cervical ganglion (SCG decentralization) protects against the allergen-provoked pulmonary inflammation. In contrast, this denervation enhances the hypotensive response to endotoxin. Since removal of the submandibular glands (submandibularectomy) abolishes the protection offered by decentralization against allergen-induced pulmonary inflammation, the sympathetic innervation to the glands inhibits the release of anti-inflammatory factors from the glands that normally modulate hypersensitivity reactions. In contrast, submandibularectomy itself enhances the hypotensive response to endotoxin and does not further modify the response seen in decentralized animals. This observation suggests that sympathetic innervation to the glands promotes the release of anti-inflammatory factors that intervene in endotoxic reactions.*

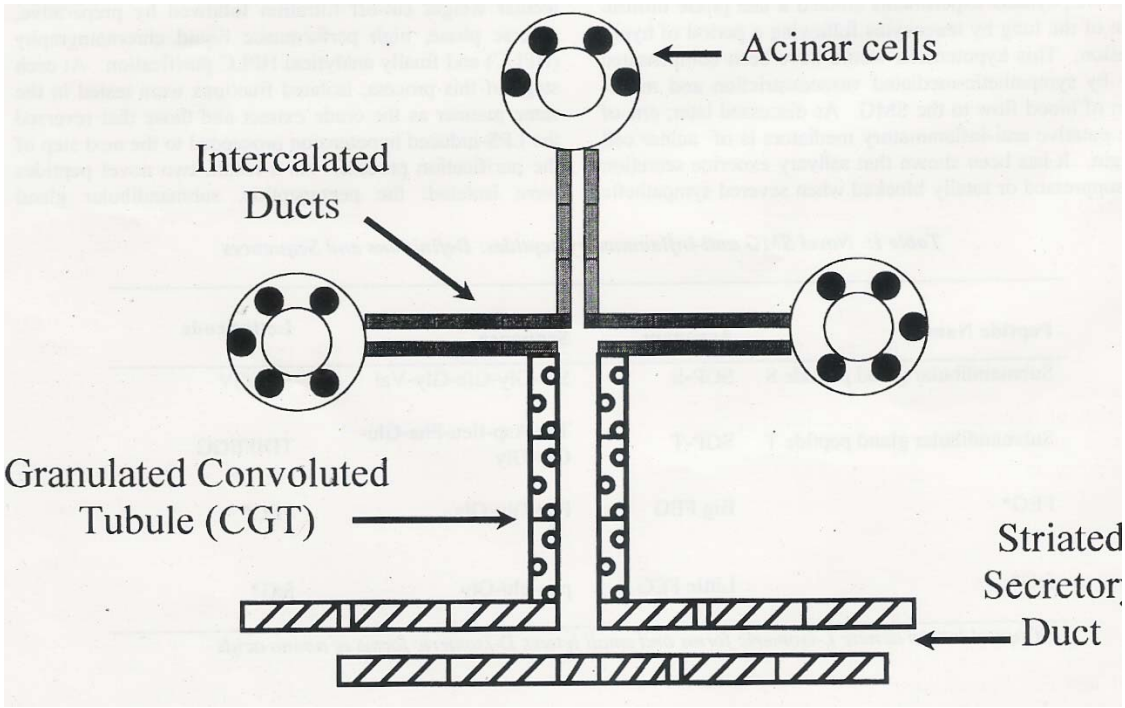

Fig. 2*: Schematic presentation of the four major epithelial compartments of the submandibular gland*

Table II: Effects of Salivary Gland Peptides (SGP-T and feG) on Physiological and Immunological Function

Function	Peptide	Inhibitory Effect	Concentration	Comment (ref)
Anaphylaxis (Rat)				
Cardiovascular	feG & SGP-T	70-80%	100 μg/kg	Hypotension [14,38,41,43]
Intestinal	feG & SGP-T	70-80%	35-100 μg/kg	Intestinal motility [16,41]
Pulmonary	feG	70-80%	1-1000 μg/kg	Pulmonary inflammation [39,40]
Endotoxemia (Rat)				
Cardiovascular	SGP-T	60-90%	35-100 μg/kg	Hypotension [15,38,46]
Intestinal	SGP-T	50%	35-100 μg/kg	Intestinal motility [47]
Intestinal	FeG-NH_2	80%	1-35 μg/kg	Intestinal motility [44]
Fever	SGP-T	Late fever $0.37^{\pm}$ $0.1^{o}C$	100 μg/kg	Endotoxin 150 μg/kg [47,48]
Effects on Leukocytes (Rat)				
Leukocyte Rolling	feG & SGP-T	70-80%	1 μg/ml	LPS and histamine onto mesentery [43]
Chemotaxis (in vitro)	FeG	25-35%	100 μg/kg	Subcutaneous carrageenan sponge [49]
Chemotaxis (in vivo)	feG & feG(NH_2)	90%	10-100 μg/kg	24h after Ag challenge [27,49,50]
Adhesion	FeG	80-90%	10^{-9}M	Leukocytes to atrial tissue [27]
TNF production	FeG	90%	1000 μg/kg	Bronchoalveolar cells after Ag challenge
Intersitial leukocytes	feG,SGP-T, FEG	--	100 μg/kg	CD18 expression [51]
CD11b expression	FeG	30-40%	10^{-10} to 10^{-11}M	PAF (10^{-9}M) stimulation [39]
Effects on Neutrophils (Human) (unpublished data)				
Chemotaxis	FeG	30-40%	10^{-9} to 10^{-11}M	PAF (10^{-9}M) stimulation
Adhesion	FeG	30-50%	10^{-9}M	Eosinophil and neutrophil to gelatin
CD11b expression	FeG	30-40%	10^{-10} to 10^{-11}M	PAF (10^{-9}M) stimulation
CD16b expression	FeG	40-60%	10^{-10} to 10^{-11}M	PAF (10^{-9}M) stimulation

peptide S (SGP-S) with an amino acid sequence SGEGV and the heptapeptide, submandibular gland peptide T (SGP-T) with a sequence TDIFEGG (Table 1).These findings were contrary to initial expectations that the anti-inflammatory mediators would be one of the established peptide regulatory factors such as EGF or NGF, localized in and released from GCT cells [1,2]. The second surprise was the probable site of release of this peptide. The SMG consists of four epithelial compartments: The acini, intercalated ducts, granular convoluted tubules (GCT) and striated secretory ducts (Figure 2). The acinar cells secrete amylase and a NaCl-rich fluid. This primary secretion is then modified by the intercalated ducts (which also contain stem cells that produce acinar cells and GCT cells during development) and the secretory ducts by the addition of a HCO_3^- rich secretion. It is the GCT cells that are considered to represent the endocrine portion of the SMG releasing many biologically active peptides such as EGF, NGF and TGFβ [1,2]. In contrast SGP-T, although a putative systemic regulator of immune function, would appear to be of acinar cell origin based on the identification of the probable gene responsible for its production.

The discovery of a Variable Coding Sequence-1 (VCS-1) gene encoding a 146 amino acid protein [32] resulted in the identification of a new prohormone (SMR1) synthesised by the acinar cells of rat submandibular glands. Proteolytic processing of the SMR1 prohormone yields smaller peptides generated from two distinct regions of the prohormone. Three structurally related peptides, namely SMR1-undcapeptide, -hexapeptide and -pentapeptide, are generated from the SMR1 precursor by specific cleavage at dibasic sites near the amino terminus of the prohormone (amino acids 20-32) [33,34]. These peptides are released from the salivary glands into the circulation and saliva following sympathetic stimulation and are believed to function as endocrine regulators of mineral homeostasis [35]. In contrast, the sequence of SGP-T is located on the carboxyl terminus of the SMR1 prohormone (amino acids 138-144). That the VCS-1 gene, and hence the SMR1 prohormone, are the precursors of SGP-T is supported by the fact that they all show the same sexual dimorphism. The gene and the SMR1 protein are expressed in the acinar cells of the male but not the female rats [36]. The putative anti-inflammatory mediator of the CST-SMG axis, which

would appear to be SGP-T, shows the same sexual dimorphism [22]. However, in order to establish definitively that SGP-T is indeed generated from the SMR1 precursor it is important to identify the precise proteolytic events producing the appropriate cleavage. In the case of SGP-T this would not be at single or paired basic residues but at pairs of hydroxylated residues such as a Ser-Thr bond [8]. This could be achieved by a recently characterised protease, subtilism/ kexin-isozyme which although widely expressed is particularly abundant in rat SMG [8] or by non arginine-dependent serine proteases that are also abundant in submandibular glands [37]. In addition, further studies on the synthesis of SGP-T and its pattern of release into the circulation will be required before its physiological role as an endocrine immunoregulatory mediator can be verified. However, the evidence to date is strongly suggestive that SGP-T is one of the endogenous endocrine mediators of the CST-SMG immunoregulatory axis and that it is produced in, and released from, the acinar cells of the SMG following proteolytic processing of the SMR1 prohormone.

Physiological and Anti-inflammatory Properties of SGP-T and Its Analogues

Further evidence that SGP-T is an endocrine mediator of the CST-SMG immunoregulatory axis is provided by a consideration of its physiological and anti-inflammatory properties, which have been studied in several animal models (unlike SGP-S which has only been assessed in the endotoxic shock model used in the original isolation studies). First, as described above, it reverses the effects of sialectomy on LPS-induced hypotension. In fact it also reduces LPS-induced hypotension in non-sialectomised rats [38]. In addition, the derivative of SGP-T (feG) mimics precisely the actions of the putative endocrine mediator postulated in the early studies on the effects of SCG decentralisation and sialectomy on anaphylaxis-induced pulmonary inflammation, namely that it suppresses the infiltration of the lung parenchyma by leucocytes (neutrophils, eosinophils and macrophages) following antigen challenge in sensitized rats. Using a different model, the ovalbumin-sensitised brown Norway rat rather than the Nb-sensitised rat, it has been shown that feG, (see Table 1) inhibits pulmonary infiltration by leucocytes following ovalbumin exposure [39,40]).

Since the isolation and identification of SGP-T, a large number of studies have been conducted in several models of shock and inflammation utilizing the parent molecule or its derivatives and analogues (such as FEG and feG). For example, when given intravenously SGP-T and/or FEG or feG will attenuate anaphylaxis and LPS induced-hypotension; inhibit the disruption of the intestinal migrating myoelectrical complex and the development of diarrhea during intestinal anaphylaxis; inhibit neutrophil adhesion to cardiac atrial slices following exposure to PAF and down-regulate neutrophil chemotaxis [27,41]. The D-isomeric form of FEG (feG) was also active in these models. Interestingly, the down-regulation of neutrophil chem. otaxis was one of the postulated properties of the putative SMG anti-inflammatory hormone based on an earlier study [42]. A summary of some of the most striking actions of SGP-T, FEG and feG *in vivo* and *in vitro* are shown in Table II. In brief, these data support the concept of SGP-T as one of the mediators of the CST-SMG regulatory axis. They indicate that these SMG peptides are potent anti-inflammatory, and anti-shock mediators effective at low concentrations and doses and are potential prototypes for the development of novel therapies.

Mechanisms of Action

In addition to their ability to down-regulate neutrophil chemotaxis these peptides also inhibit leukocyte rolling and adhesion (43) suggesting that they exert their anti-inflammatory effects by inhibiting cell to cell interactions. This appears to be the case. Intraperitoneal administration of feG inhibits LPS-induced expression of integrins such as CD18 on tissue resident leucocytes and reduces the influx of leucocytes into the peritoneal cavity [44,45]. They also inhibit at low doses (10pM) PAF-induced expression of cell surface molecules involved in chemotaxis such as CD11b and CD16b.

Summary

The evidence presented above demonstrates that the SMG is an integral part of the body's neuroendocrine immunoregulatory system. It is regulated by the central nervous system via the sympathetic division of the autonomic nervous system. Its ability to inhibit shock and inflammatory responses to several stimuli is probably due to the release of potent anti-inflammatory mediators from the SMG. These are small peptides; probably derived from the SMR1 prohormone in the acinar cells and they exert their effect through the inhibition of chemotaxis and the adhesion, extravasation and activation of leucocytes as a consequence of interference with the activity or expression of integrin molecules on leukocytes.

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