IMMUNOREGULATION BY THE SALIVARY GLANDS

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SUMMARY

The evidence for the integration of the submandibular gland (SMG) into the neuroimmunoregulatory network is reviewed. In laboratory rodents, factors extracted from the SMG were shown to stimulate lymphocyte proliferation, to affect the weight of the thymus, spleen and lymph nodes and to induce immunosuppression in several in vivo and in vitro models. The SMG produces significant amount of nerve growth factor (NGF), epidermal growth factor (EGF), transforming growth factor-β, and kallikreins. These factors are secreted into the saliva and affect immune and mucosal tissues and nerve endings in the gastrointestinal tract. They may thus play a role in the regulation of mucosal immune/inflammatory responses. The major salivary glands also produce antimicrobial proteins and secretory IgA antibodies which are essential factors in mucosal host defence. SMG-derived NGF, EGF and glandular kallikrein are delivered into the bloodstream where they may act as important systemic immunoregulators and exert regulatory influences on the neuroendocrine system. Growth hormone, prolactin, androgens, thyroid hormone and corticosteroids regulate protein synthesis in the SMG, whereas secretory activity is regulated by sympathetic, parasympathetic and peptidergic nerve fibres. Steroid hormones and cytokines as interleukin-la, -1β, tumor necrosis factor-α, interferon-y have major regulatory influence on protein secretion, including the secretion of immunoglobulin into the saliva. The SMG interacts with the mucosal and systemic compartments of the immune system, with the central and peripheral nervous systems, with the pituitary gland, and with peripheral endocrine organs. These interactions enable the SMG to exert regulatory influences on immune/inflammatory reactions in the gastrointestinal tract, in the lungs, and possibly elsewhere. It is suggested that these functions make this gland a key regulatory organ in the neuroimmunoregulatory network. (Biomed Rev 1998; 9: 79-91)

INTRODUCTION

Ever since the classical studies of Pavlov, it is of common knowledge that the function of the major salivary glands is intimately regulated by the central nervous system. It is now certain that the salivary glands also perform an important immunoregulatory function, and that immune reactions can be conditioned in the Pavlovian sense (1,2). Early studies showed that the submandibular gland (SMG) produces, stores, and releases biologically active molecules, such as kallikrein (3), nerve growth factor (NGF) (4), and epidermal growth factor (EGF) (5), which are now known to regulate immune reactions. It has also been demonstrated that the function of the SMG is regulated by hormones. In the 1960s, SMG extracts were found to reduce the weight of the thymus and lymphoid organs (6) and to produce immunosuppression (7). The role of the major salivary glands in immunoregulation and in the neuroimmunoregulatory network is poorly defined. Here we review the possible role of the SMG in the neuroimmunoregulatory network, providing the available evidence in order to clarify some key questions and identify others that need to be answered.

THE SALIVARY GLANDS

Major salivary glands, including the SMG, parotid and sublingual glands, and minor glands associated with the oral
mucosa, may be distinguished in mammals. The glandular epithelial cells may be divided into two functionally distinct groups, acinar and ductal. The secretory end piece consists of acinar cells of one or two types. These cells generate all the saliva fluid and approximately 85% of the excreted proteins from the gland. The fluid is derived from the vascular bed and is isotonic at this stage. In the SMG, the acini are connected to each other by intercalated ducts which lead to the granulated convoluted tubules which in turn join into the striated excretory duct. Ductal cells reabsorb from the primary saliva most of the Na+, Cl− while secreting small amounts of K+ and HCO3−.

Ductal cells also secrete proteins into the saliva which is markedly hypotonic by the time it enters the mouth. Salivary gland secretion is under neural control. The glands receive sympaticic, parasympathetic and peptidergic innervation. Sympathetic stimulation leads to high levels of protein secretion and parasympathetic stimulation induces fluid output. Acinar cells have α-, β-adrenergic, and muscarinic cholinergic receptors and receptors for vasoactive intestinal peptide (VIP), substance P (SP), prostaglandins and many peptide hormones, including vasopressin and parathyroid hormone. Cyclic AMP, G-proteins P (SP), prostaglandins and many peptide hormones, including vasopressin and parathyroid hormone. Cyclic AMP, G-proteins P (SP), prostaglandins and many peptide hormones, including vasopressin and parathyroid hormone.

The macromolecules present in saliva fall into various families: histatins (2-4 kD), statherins (4-5 kD), lysozyme (14 kD), cystatins (14 kD), proline-rich proteins (10-30 kD), carbonic anhydrases (42-45 kD), amylases (55-60 kD), peroxidases (75-78 kD), lactoferrin (75-78 kD), mucinNo2 (130 kD),-secretory IgA (380 kD), α-defensins (75-78 kD), and mucinNo 1 (>1000 kD). These proteins are multifunctional and participate in buffering (carbonic anhydrases, histatins), digestion (amyloses, mucins), mineralization (histatins, proline-rich proteins, statherins), lubrication and viscosity (mucins, statherins), tissue coating (amyloses, cystatins, proline-rich proteins) and many possess antimicrobial properties.

IMMUNOREGULATORY FACTORS OF THE SUBMANDIBULAR GLAND

• The SMG produces numerous biologically active polypeptides which may be classified into three major groups: (i) growth factors, such as EGF and NGF, (ii) homeostatic peptides, such as kallikrein and renin, and (Hi) regulatory poly peptides, such as transforming growth factor-β (TGF-β), glucagon and cytokines. Polypeptides of the first two groups are stored in sercretion granules of the convoluted tubular cells and are frequently released separately. Peptides of the third group have a less well-defined localization and the secretion patterns are not well studied. Here we restrict our discussion to those factors that have a well-defined immunological effect (Table 1).

• Transforming growth factor β-1

TGF-β3 is a dimeric peptide presenting several isoforms. The growth promoting effect of TGF-β is likely to be indirect through the stimulation of new extracellular matrix, changes of adhesion molecules and the alteration of growth factor secretion by various cells (13). Thus TGF-β should be considered a regulatory cytokine that exerts a complex effect on inflammatory and immune responses. It acts as a chemoattractant for monocytes (14), neutrophils (15-17) and lymphocytes (18), and activates monocytes to secrete cytokines and growth factors (14,19). Later, activated monocytes downregulate the number of their TGF-β receptors and become refractory or even suppressed by this cytokine (20). TGF-β stimulates inflammation at the beginning while later supports its resolution and contributes to healing. Resting T cells are not affected significantly by TGF-β, while activated CD4+ T cells are suppressed (21,22) and CD8+ T cells are stimulated (23,24). B cell proliferation and the production of IgG and IgM are suppressed (25,26). TGF-β also supports the switch of antibody response to IgA production (27-29).

• Epidermal growth factor and related molecules

EGF and TGF-β, both of which are present in the SMG, have a similar biological effect and bind to the same type of receptor, a 170 kD molecule which is usually referred to as the EGF receptor (30-32). EGF and TGF-β function as growth factors for epithelial cells and fibroblasts (33) and are considered important for the maintenance of mucosal integrity (34-39). EGF stimulates T cell proliferation, increases the production of interferon-γ (IFN-γ) and reduces T suppressor cell activity (40-42). EGF stimulates macrophages for chemotaxis and phagocytosis (43,44). These activities suggest that EGF is immunostimulatory and proinflammatory. Nevertheless, EGF was shown to suppress delayed-type hypersensitivity (DTH) reactions (45).

• Nerve growth factor

NGF was first described in the mouse SMG (46). It stimulates the growth of sympathetic ganglia which innervate immune organs (47). NGF was shown to increase the number and size of mast cells in tissues of neonatal mice (48), and stimulate histamine release from mast cells, both in vivo (49) and in vitro (50,51). NGF also stimulates the development of hemopoietic colonies (52, 53) and increases phagocytosis and chemotaxis of neutrophils (52,54). These effects of NGF should suggest a proinflammatory role, yet NGF was shown to suppress in vivo inflammatory reactions in several models (55,56). The reason for this paradox is at present not known. NGF receptors are present on both B lymphocytes and antigen presenting cells (57-59). Likewise, lymphocyte growth is stimulated by NGF in vitro (60-62). Production of IgM (62) and IgG4 (63) by human B cells is enhanced by NGF, but other IgG subclasses are not affected.
Immunoregulation by salivary glands

Table 1. Main immunological effects of some submandibular gland factors

<table>
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<tr>
<th>Factor</th>
<th>Effect</th>
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<tr>
<td>TGF-β</td>
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<td>Activation of monocytes</td>
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<td></td>
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<td>Antinflammatory activity in vivo</td>
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<td>Chemotaxis and stimulation of phagocytic activity of neutrophils</td>
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<td></td>
<td>Stimulation of lymphocyte proliferation</td>
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- Kallikreins

Kallikreins are proteolytic enzymes which belong to the family of serine proteases. There are 20 kallikrein genes in rodents (64). Of these, at least 6-7 genes are expressed in the rat SMG (65). Plasma kallikrein differs in molecular weight and enzymatic activity from tissue or glandular kallikreins. Members of the latter group are differentially expressed in different tissues (64). In this review we designate the product of the hRK ALL gene in humans, the mGK-6 gene in the mouse, and the rGK-1 gene in the rat as glandular kallikrein (GK) (66). In addition, the general term kallikrein will be used for any unspecified member of the kallikrein family. The best studied substrate for GK is kininogen produced by the liver (66), which has two forms: low molecular weight kininogen (50 kD) and high molecular weight kininogen (120 kD). Plasma kallikrein produces the nonapeptide bradykinin from kininogen. On the other hand, GK gives rise in most other species to a decapeptide, kallidin (Lys-bradykinin), which is biologically active but may also be further processed into bradykinin. In the rat, GK has been reported to produce bradykinin (67). GK may activate or regulate other immunologically active factors of the SMG, including NGF, EGF/TGF-oc and TGF-β3. In extrasalivary tissues, GK may also process other important molecules, such as prolactin (68,69).

Kallikrein has a mitogenic effect on both thymocytes and T and B lymphocytes (70) and was shown to be involved in Ig isotype control. Ishizaka (71) described a kallikrein-like factor, glycosylation-enhancing factor, which induced CD4+ T cells to produce IgE potentiating factor and favoured IgE production. Serine proteases from Schistosoma mansoni schistosomula enhanced IgE production (72). In vitro, the addition of kallikrein and other serine proteases to B cells stimulated with lipopolysaccharide and IL-4 enhanced the production of IgE, IgG 1 or IgG3 (73). Experiments in our laboratories demonstrated that a 40 kD protein from the rat SMG induced the stimulation of in vitro...
lymphocyte proliferation and the suppression of in vivo immune reactions (74). The purified 40 kD protein catalyzed the hydrolysis of N-benzoyl-arginine ethyl ester. This esterase activity was inhibited by the protease inhibitor aprotinin. The sequence of the first 25 amino acids demonstrated that this protein was rat glandular kallikrein (rGK). When added to cultures of murine lymph node cells suboptimally stimulated with the T cell mitogen concanavalin A, rGK markedly stimulated the proliferative activity of these cells (Fig. 1). When injected into mice, rGK suppressed the DTH response to picryl chloride (Fig. 2), and the plaque-forming cell reaction in the spleens of animals immunized with sheep red blood cells (75). Similar effects were induced with glandular kallikrein from porcine pancreas (pGK). Moreover, the in vitro and in vivo effects were abolished by aprotinin either added to the tissue culture medium or injected into the animals immediately before rGK or pGK. This gave further support to the conclusion that the immunological effects we observed were due to activity of rGK and indicated that rGK may act via the mediation of some product(s) of its enzymatic activity on an as yet unidentified substrate.

**THE IMMUNE FUNCTION OF SALIVARY AND LACRIMAL GLANDS**

- The salivary and lacrimal glands secrete antimicrobial proteins, antibodies and cytokines, which play an important role in host defence by natural immune mechanisms. Specific immune defence is also mediated by these glands primarily by the secretion of IgA antibodies. In the saliva, amylase, cystatins, histatins, mucins and peroxidases, have antibacterial, antiviral (cystatins and mucins) and antifungal (histatins) effects (10). C-reactive protein (CRP) is also present in saliva (76) and has the capacity to combine with surface moieties of diverse microorganism followed by immune activation and the stimulation of an inflammatory response (77). There is a correlation between salivary and serum CRP levels in man (76). In the salivary gland, IgA is produced by plasma cells and secreted by ductal acinar cells that express surface receptors (secretory component, SC) for polymeric IgA molecules. IgA combines with SC on the epithelial cell surface, and is internalized and released onto the mucosal surface. The salivary glands are part of the "common mucosal immune system " which provides defence of mucosal surfaces. After antigenic stimulation at a certain mucosal site, IgA forming cells enter the blood stream via the thoracic duct and redistribute to other sites. Thus, the external secretions of glands will contain IgA antibodies specific for the antigen at sites that are anatomically remote from the primary site of stimulation. This is valid for B cells producing immunoglobulins other than IgA. For this reason, the analysis of salivary antibodies can be used to provide a general picture of mucosal immunity (78-82).

Some epithelial cells express majorhistocompatibility complex (MHC) class I in salivary and lacrimal glands of rats. MHC class II is expressed only by the glandular epithelium of SMG and by dendritic cells in all glands (83). Graft-versus-host reaction increased the expression of MHC in the rat SMG (84). The glandular expression of MHC II in humans was associated with Sjogren's syndrome (SS), symptomatic xerostomia, rheumatoid arthritis, and systemic lupus erythematosus. Expression was confined to epithelial cells in close proximity to lymphocytic infiltrates (85,86). Helper T lymphocytes for cell mediated (Th1) and humoral (Th2) immunity are both present in the SMG (87). In addition to T lymphocytes, mucosal epithelial cells are also producing immunoregulatory cytokines, such as IL-6 and TGF-P. Production was significantly upregulated as a consequence of local infection (80). Cytokines also regulate glandular epithelial cells, e.g. IFN-inhibits epithelial cell growth that is synergistically enhanced by TNF-a (8). The secretory component plays a critical role-limiting role in the secretion of polymeric IgA onto mucosal surfaces. This process is regulated by hormones, such as androgens, estrogens, progestins, glucocorticoids, prolactin, and thyroid hormone, neurotransmitters and neuropeptides (adrenergic and cholinergic transmitters, VIP) and by cytokines (IL-1 a, -1, 1, 3, TNF-a, IFN-y) in a tissue- and organ-specific manner. Thus in the lacrimal gland, androgen, VIP, the adrenergic agonist isoproterenol, IL-1, -3, and TNF-a all are
Immunoregulation by salivary glands

Figure 2. Effects of rGK and pGK on the DTH response of A/J mice immunized with picryl chloride and reversal of such effects with aprotinin. Aprotinin (Apr) was injected sub-cutaneously as a full dose (190 µg per animal) or as a half dose (95 µg per animal). Fifteen minutes later the animals received a further subcutaneous injection of rGK or pGK in 0.2 ml of PBS or PBS only. Results are expressed in terms of the increase of the thickness of the challenged ear over the prechallenge values. Unimmunized controls (not shown) did not show any increases of the ear thickness.

Subsequent experiments showed that combined treatment with thyroid hormone, testosterone and prolactin results in maximal restoration. Thus the SMG has been identified as a new prolactin target. Other investigators observed that the immunomodulatory function of the SMG is regulated by the superior cervical ganglion (8,99,100). The possibility was also raised that not all functions of the SMG are under sympathetic control (101,102).

ENDOCRINE REGULATION OF SUBMANDIBULAR GLAND FUNCTION

- The SMG is more developed in males than in females and it regresses in castrated males (103-105). Androgens, thyroid and adrenocortical hormones are necessary for the normal development of the gland and for the production of biologically active polypeptides (106-108). In rats, NGF, EGF, kallikrein, insulin (10,109,110), renin (111), and the production of various enzymes have been shown to be dependent on sex hormones and thyroxin. EGF, NGF and kallikreins are produced by the glandular cells of the convoluted tubules (112). Insulin and GK seem to be preferentially produced in the intercalated tubes (113) and other factors may be produced by acinar cells (114).
- Specific induction of certain factors by certain hormones and different responses among various animal strains of the same species are possible (115). The SMG affects testicular function either by acting on the hypophysis or via EGF (116-121). It also affects the uterus by the modulation of ovarian hormones (122).

NEURAL REGULATION OF SUBMANDIBULAR GLAND SECRETIONS

- The SMG receives both sympathetic and parasympathetic nnervation. The parasympathetic system stimulates the glandular acinus leading to the secretion of large volumes of saliva with low concentrations of biologically active polypeptides (123-125). P-adrenergic stimulation increases the synthesis and release of these polypeptides (114,126,127). The secretion of both growth factors and homeostatic proteases by the convoluted tubules is stimulated by a-adrenergic agents (128), which leads to the appearance of large amounts of kallikrein (129),NGF(130),EGF(131),andrenin(1) 32 in the saliva, whereas a-adrenergic agents exert a significantly lesser effect. However, a-adrenergic agents do not increase NGF release into the bloodstream. In rats, the electrical stimulation of the sympathetic trunk leads to a large increase of kallikrein in the saliva and bloodstream, while parasympathetic stimulation is ineffective (133,134). The effect of sympathetic stimulation may be blocked by α1-adrenergic antagonists (135). a-adrenergic agonists significantly increase salivary excretion, but not the endocrine release of kallikrein, while P-adrenergic agonists induce a lesser effect, and cholinergic agents are ineffective. These results led to the suggestion that the endocrine secretion of

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kallikrein requires both cc-adrenergic stimulation and another as yet unidentified neurotransmitter (136). A smaller but significant constitutive release of kallikrein into the blood has been demonstrated (135), as well as a similar dual endocrine regulation of NGF and EGF (137) and of renin (138) release was also observed in mice.

THE SALIVARY GLANDS AND DISEASE

- The analysis of saliva is informative with regard to general health and also reflects environmental influences. Through salivary analysis one may obtain information regarding (i) tissue levels of drugs, (ii) emotional status, (iii) hormonal status, (iv) immunological status and immune responsiveness, (v) neurological status, and (vi) nutritional and metabolic conditions. Accordingly, salivary gland analysis is useful in a number of medical problems (13, 9, 140, 140a). The salivary glands are often affected by inflammatory disease (141). In man, the most frequent inflammatory disease of the salivary and lacrimal glands is Sjogren's syndrome (SS). This is characterized by lymphocytic infiltration of the gland and the presence of plasma cells producing IgA autoantibodies. The disease shows a female prevalence and may lead to the failure of salivary and lacrimal glands causing xerostomia and keratoconjunctivitis sicca, respectively. Although SS may occur as an isolated disease, it is frequently associated with systemic immune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and sarcoidosis. Immune complexes, autoantigens and, more recently, retro viruses (HTLV-1, HIV) have been proposed as causative agents of SS (142-147). Transgenic mice carrying the tax gene of HTLV-1 develop exocrinopathy which resembles SS (148). Lacrimal and salivary gland inflammation occurs in spontaneous autoimmune mice carrying the lymphoproliferative (lpr) gene. Salivary gland inflammation correlates positively with serum immune complexes in such mice. A number of other autoimmune mouse strains develop SS-like disease: MRL/lpr, NZB, NZB/NZW, BDF1, non-obese diabetic (NOD), and Palmerston North (149). In mice, experimental graft-versus-host disease leads to sialoadenitis in their SMG, characterized by mononuclear infiltration with T cell predominance (150). The salivary glands of autoimmune MRL/lpr mice are infiltrated predominantly by T cells which show oligoclonality (151). In these animals, CD4+ T cells play an important role in the pathogenesis of SS-like disease, as is the case in patients with SS (152). Autoimmune sialoadenitis may be induced in Lewis rats by immunization with salivary tissues in which CD4+ T cells play a pathogenic role (153). Salivary gland inflammation and lymphocytic infiltration in female MRL/MpJ-lpr/lpr mice was significantly reduced by treatment with 19-nortestosterone, testosterone, cyclophosphamide or dexamethasone. The infiltration of the lacrimal glands was reduced by 19-nortestosterone or cyclophosphamide (154). Other immune/inflammatory diseas es of the salivary gland in man are benign lymphoepithelial lesions (Mikulicz's syndrome) (155), allergic submandibular salivary disease (156), lymphadenopathy in the submandibular, submental and upper cervical region (Kimura's disease) (157), and salivary Wegener's disease caused by autoantibodies to neutrophil leukocytes (158).

EGF shows a diurnal rhythm in human saliva but not in serum. Salivary EGF levels are increased in patients with inflammatory disease or with head and neck tumors (159, 160). The induction of novel cells forming small glands around gastrointestinal ulcers which secrete EGF has been described in man (161). In the saliva of patients with gingivitis and periodontitis, cystatin S and C were found to be elevated (162).

NOD mice show lymphocytic infiltration and glandular disorganisation of the SMG coupled with a profound reduction of EGF in the gland (163). Streptozotocin-induced diabetic mice show low serum EGF levels and develop oligoospermia. EGF treatment increased sperm count and treatment with insulin restored the SMG, plasma EGF concentration and sperm counts to normal levels (164). In the salivary gland of NOD mice, 3-adrenergic receptors are downregulated (165). Amylase levels were reduced significantly in the parotid gland and pancreas of diabetic rats which could be reversed by insulin (166).

CONCLUSION

- Mucosal membranes are constantly exposed to antigenic material, microbes, irritants, and toxins. Under these conditions, an exaggerated response to harmless food or airborne antigens is just as dangerous as an insufficient immune response to pathogenic agents. Much of mucosal immune defence takes place on the surface of mucous membranes, which falls outside of the body. Therefore, self-nonself discrimination by the immune system is not sufficient for host defence. For this reason, neuroimmunoregulatory factors should play a primary role in assuring that harmless antigens are tolerated, whereas adequate defence is mounted against pathogens. The predominance of tolerance induction against orally introduced antigens is firmly established in immunology (167-169). Animal experiments indicate that the induction of oral tolerance may even be useful for the treatment of some systemic immune disorders. It appears that differences in antigen presentation by epithelial cells and of the cytokines involved play an important role in deviating the immune response against orally administered antigens towards suppression rather than immunity (167). Oral treatment with the specific antigen inhibits autoimmune disease in experimental animals. This information coupled with the observation that systemic autoimmune disease is often associated with SS, suggests that immune-regulation by the major salivary glands plays an important role in systemic immunoregulation. The major salivary glands are ideally suited to provide the host with the first line of mucosal defence. It is likely that saliva-
Immunoregulation by salivary glands

Some important questions with regard to the role of the SMG in the neuroimmunoregulatory network remain unanswered. For instance, we do not know the details of immunoregulation by salivary factors. It is not known of whether local regulation mediated by saliva or the systemic immunomodulatory effect of SMG is predominant. It is not dear whether immunoregulation by major salivary glands is essential for immune homeostasis or it is redundant in nature. The question is further complicated by the existence of sex- and sex-related differences. The salivary regulatory factors may exert a systemic effect by (i) direct endocrine release from the glandular tubular cells, (ii) through reabsorption from the intraglandular ducts, or (iii) reabsorption from the gastrointestinal tract after swallowing (70). These possibilities remain to be investigated. It has been observed that the blood in the veins draining the SMG contained more kallikrein than the arterial blood and that both kallikrein and tonin levels increased in the venous blood of SMG after sympathetic stimulation (134, 170). Ductal reabsorption is suggested by the finding that $^{125}$T-kallikrein enters the blood after retrograde injection into the excretory duct (171). Immunochemical studies in mice suggested that kallikrein and renin are constitutively secreted from the basolateral surface of tubular cells and reach the blood via fenestrated endothelium underlying the ducts (172). At least some factors secreted in saliva exert direct effects on mucosa-associated tissues. The effect of EGF on the buccal and gastric mucosa is particularly documented (34,35) and supports this possibility. Also, cells of mucosal lymphoid tissues (173) and tooth pulp (174) possess NGF receptors. Another such factor may be GK which is probably resistant to digestion by enteric proteases (66) and thus may be able to exert its effect in lower parts of the gastrointestinal tract. The effects induced by salivary regulatory factors on intestinal lymphoid cells may affect other lymphoid organs via lymphocyte recirculation (175). Most of the biologically active factors produced by the SMG may be found in other tissues. The extirpation of SMG either failed to produce significant decrease in levels of EGF (131), NGF (176) or renin (177,178) in the serum or caused only transient reductions followed by recovery to normal values. This suggests that the SMG has a contributory role in immunoregulation by these factors. However, because of its strategic location, the SMG and other salivary glands are capable of dramatically increasing the output of these regulatory factors into the saliva and possibly also into the blood under the influence of the autonomic nervous system (135). In fighting mice, for example, NGF level was significantly elevated in the blood and affected the adrenal glands, mast cells, behavior and inflammatory reactions (see 179, Aloe and Fiore, this volume of Biomedical Reviews). The interaction of the SMG with the gonads and the regulation of SMG and immune functions by sex hormones is intriguing. Factors secreted by the SMG appear to affect gonadal and adrenal function. Actually the SMG may affect immune responses through this pathway. Some SMG factors show marked species related differences. Tonin, an enzyme in the kallikrein family, for example, is present in large amounts in the rat SMG (65) but has not been demonstrated in other species. Renin was found in murine SMG but not in the rat (180). NGF is contained in large amounts in mouse SMG (46,47), whereas the human gland contains smaller amounts. In contrast, the human parotid secretes six-fold more EGF than the SMG (159). Some other factors, such as kallikrein and EGF, have been found in several species, including man, rat and mouse. The immunoregulatory effects of SMG extract have also been observed in various species, such as rat, mouse and cattle (181). Although it is clear that species related differences exist, it appears that the SMG and perhaps some of the other salivary glands, perform an important immunoregulatory function in all the mammalian species so far examined. The sex dimorphism in SMG function and regulation appear to be quantitative rather than qualitative. The female gland is smaller in many species and consequently contains less biologically active factors. Differences in immune responsiveness of males and females are also well known. It is possible that some of these differences may be explained in the future by the different ability of the SMG to secrete regulatory factors.

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