THE SUBMANDIBULAR GLANDS: A ROLE IN HOMEOSTASIS AND ALLOSTASIS

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SUMMARY

• *The salivary glands are important exocrine and endocrine organs, whose role in oral health is well recognized. Only within the last 15 years has it become apparent that these glands also contribute to maintenance of systemic health. Salivary gland polypeptides promote health and well-being by aiding in wound healing, rnucosal protection, tissue and organ regeneration, and immunomodulation. It is proposed that salivary gland factors form an integral part of the body's homeostatic processes. In the their absence, a condition promoted by many diseases or by artificially removing the glands (sialadenectomy), oral and systemic health is jeopardized. When the salivary glands do not secrete their hormones properly the organism is no longer able to normally regulate several functions since important homeostatic mechanisms become dysfunctional. This breakdown in homeostatic mechanisms results in the establishment of an alternative state, that of allostasis, which is generally associated with illness or susceptibility to illness. It is proposed that the dysfunctional salivary glands facilitate the development of the pathologies associated with various disorders, such as diabetes mellitus and enhanced sensitivity to endotoxin.*

INTRODUCTION

• Some 20 years ago the immune system was generally considered to operate independently and autonomously in protecting the body from unwelcomed invaders and injury. In the mid-1970's, the application of immunological tools to investigations of neural and endocrine problems (1) led to a revolutionary concept: the immune system is a special adaptive mechanism that is intimately integrated with other neuroendocrine homeostatic processes. This new immunological perspective revealed an unexpected complexity in the interactions between behavioral, neural, endocrine and immune processes (2). It is now acknowledged that the body's defence system, an integral part of homeostatic processes, involves an intricate system of neural, endocrine, paracrine and autocrine communication.

With the advent of the neuroendocrineimmunological paradigm it has become apparent that the traditional roles assigned of certain glands and organs need to be reexamined. One such glandular system that has acquired importance, in view of the fine control exerted by neuroimmunological integrator mechanisms, is the salivary glands. Once regarded as an accessory digestive organ, the salivary glands are in actual fact a rich source of biologically active peptides that play an important role in the maintenance of healthy tissues and participate in growth and differentiation, inflammation and wound healing (3-5). Salivary gland dysfunction probably contributes to the development and maintenance of some pathological conditions.

SALIVARY GLANDS IN HEALTH AMD DISEASE

• **Salivary glands and oral health**

The approximately 500 ml of saliva produced each day is vital for the maintenance of health and function of the periodontium. Specific components in saliva provide protection of hard and soft tissue, facilitate speech, mastication and deglutition, and

the amylases and ribonucleases found in saliva contribute to digestion. A substantial portion of the oral host defence mechanisms (antimicrobial - bacterial, fungal and viral) is mediated by families of salivary proteins: the proline-rich proteins (PRP), staterins, cystatins and histatins, which account for more than 70 % of total salivary proteins (6). Mucosal and gingival integrity is maintained by the lubricating action of salivary glycoproteins and mucins (6,7) and several poorly characterized proteins that down-regulate neutrophil function (8). Dysfunctional saliva flow, caused by systemic diseases or of iatrogenic (caused by drugs or cancer therapies) origin, generally results in poor oral hygiene (7). Furthermore, as our understanding of salivary gland function increases it is becoming more apparent that these glands have a profound impact on systemic health as well.

Q   Other functions of salivary gland secretions

Barka (3) in 1980 proposed that salivary gland secretions contribute to homeostasis. This review summarized the occurrence, chemical properties, localization, hormonal control, secretion and possible physiological roles of some 25 biologically active peptides in the submandibular glands. Since then other enzymes, growth factors, immunomodulatory factors, and peptides of unknown function have been found in salivary glands. Given the structural and functional diversity, as well as the phylogenetic conservation, of these polypeptides the fundamental question remains: "Why are they present in the salivary glands?". The exocrine secretion of these factors is very important in oral health. By recognizing that salivary gland exocrine secretions are swallowed and enter into the blood stream where they act as endocrine hormones, the fundamental importance of these glands in the regulation of systemic homeostasis becomes more evident.

•   *Wound healing*

Although epidermal growth factor (EGF) was isolated from the submandibular glands of mice based on developmental effects on eyelid opening and eruption of incisors (9), it was not recognized until much later that factors in saliva contribute to the healing of wounds to the skin (10). Interestingly, wound healing occurs more rapidly if communal grooming and licking occurred than if the mice are housed individually. Some of the salivary gland factors responsible for wound contraction are EGF (11,12), nerve growth factor (NGF) (13) and transforming growth factor-B (TGF-B) (12). These factors also contribute to the healing of intestinal lesions (14).

•   *Mucosal protection*

The salivary glands and their growth factors, in particular EGF and NGF, exert significant protective effects on the gastric

(15) and oesophageal (16) mucosa. This latter study is of particular significance since it demonstrates that the healing and protective effect of salivary gland EGF applies also to humans and is not exclusively a phenomenon restricted to rodents. An important distinction, however, is that salivary gland EGF is found predominately in the submandibular glands of rodents, but in the parotid gland of humans (17). The mucosal protective effects of salivary gland growth factors are attributable to inhibition of acid secretion and induction of tissue repair mechanisms, and possibly stimulation of mucosal blood flow (18). Nonetheless, a dissociation between mucosal protection and microvascular perfusion has been noted (19).

•   *Tissue and organ regeneration*

For a large part the exocrine secretion of growth factors into saliva accounts for the wound healing and mucosal protection and repair, although following salivary duct ligation wound contraction occurs more rapidly than in sialadenectomized animals (10). This observation, which suggests an endocrine component to the healing effects of salivary gland factors, helps explain the role of salivary factors on a variety of proliferative and differentiation events. Submandibular gland EGF promotes mammary tumor formation in mice (20). Marked effects of the salivary glands on the reproductive tract have also been noted. Sialadenectomy, which reduces circulating levels of EGF (21), results in lower uterine weights, delayed implantation and an increased abortion rate (22), although ovary weights are not affected. The same operation in male mice markedly inhibits the meiotic phase of spermatogenesis since the number of mature sperm in the epididymis and spermatids in the testis are reduced by approximately 50 %, whereas the number of spermatids in the testis increases (21). Humoral factors released from the salivary gland are also required for liver regeneration (23), and ligation of the venous drainage of the major salivary glands inhibits the increase in DNA synthesis in the remaining liver tissue following partial hepatectomy (24). This dependence of liver regeneration on the salivary glands may be due to the presence of hepatocyte growth factor in the submandibular glands (25). Other tissue protective and regenerative effects of salivary gland factors will undoubtedly be discovered.

•   *Immunomodulation*

The suggestion that the submandibular glands contain factors that can suppress immune and inflammatory reactions in rodents were first mentioned in the 1970's (26-29). More recently, some factors that either stimulate or inhibit lymphocyte proliferation (30,31), and development of normal bone marrow cell precursors (32) have been isolated from submandibular glands. Some of the better studied growth factors found in the submandibular glands, such as NGF, EGF and TGF-6,

possess immunomodulatory activities that could modify both periodontal (33), as well as systemic immune responses (3,5,34).

Nonetheless, the identification of immune modifying activities and factors within a gland does not necessarily extrapolate to the situation that the gland itself plays a role in modulating the immune response. However, experimental data support this hypothesis. Sialadenectomy results in a suppressed immune response to sheep red blood cells (35) and an inhibition of delayed hypersensitivity (36), although this latter observation is contradicted by an earlier study (29). When pathophysiological responses to immunological insults are examined it is apparent that the presence of the submandibular glands increases immediate hypersensitivity reactions in the lungs (37), but prevents the severity of the circulatory shock induced by endotoxin (38).

Thus, just as removal of the submandibular glands can affect reproduction, hepatic regeneration, the development of ulcers and wound healing, sialadenectomy has a profound influence on the ability of the immune system to respond to antigenic and toxic stimuli. The salivary glands thus appear to be involved in maintaining normal body function. This concept, which has been discussed previously (4,5,39), proposes that a neuroendocrinoimmunological circuit that is comprised of the hypothalamus, the cervical sympathetic trunk and the submandibular glands.

However, the question still remains, given the numerous and large variety of growth factors found in the salivary glands: "What role do they actually play in homeostasis?"

HOMEOSTASIS, ALLOSTASIS and RHEOSTASIS

• Homeostasis, which implies a constancy of the *"milieu interieur"* has contributed enormously to our understanding of biological processes. As developed by Cannon (40), homeostasis embraces the idea of a stable internal environment, but also emphasizes the importance of dynamic equilibria and variability. However, contemporary definitions of homeostasis highlight the "maintenance of static, or constant, conditions of the internal environment" (41). Consequently, some authors have mistakenly argued that homeostasis cannot account for the continual redefining of steady state that occurs in face of circadian, mensural and circumannual variations in physiological parameters, as well as those changes imposed by exercise, stress and disease (42,43). Sterling and Eyer (42) have proposed that the continual setting of new operating ranges of the body's vital functions is achieved by the process of *allostasis*. Accepting this definition of allostasis essentially requires that homeostasis be discarded as an operative and useful process. Rather than having the term homeostasis be-

come an archaism an alternative term, *rheostasis* proposed by Mrosovsky (44), maintains that homeostasis is valuable and physiologically relevant. Rheostasis describes "the regulation around shifting set-points" (44), that occur within a range of values compatible with homeostasis. Nevertheless, an expanded version of the concept of allostasis is useful, when put in a context somewhat different from that originally proposed (42). This new formulation requires incorporation of the idea of *allostatic load* (43).

•   **Allostatic load**

The basic proposition of allostatic load is that the continual changes in physiological functions required for the repeated resetting of steady states and operating levels, can impose a strain which predisposes the organism to disease. An example of allostatic load is combined elevation of cortisol and insulin secretion, which may accelerate the development of atherosclerosis (43,45). The problem with this definition of allostatic load is that it does not clearly distinguish between the processes (the physiological changes - elevated cortisol and insulin) and the result of these processes (atherosclerosis).

•   **Redefining allostasis**

Rather than discarding the concept of homeostasis under the pretence that constant changes in physiological variables precludes it as a valid concept, homeostasis should be viewed as encompassing the many different set points that manage the normal cyclical variations in physiology. Rheostatic processes contribute to the development of the new steady states within the homeostatic domain irregardless of their duration and stability (Fig. 1). Allostatic load then describes the processes which contribute to the movement of set points and steady states outside the domain that defines normal homeostasis, such that other regulatory mechanisms become active with the breakdown in homeostatic processes. As a consequence of allostatic load an organism may shift from homeostatic to allostatic control. Some examples of allostatic load are: the overuse of a homeostatic process (excess insulin secretion), the disappearance of a normal physiological process (the destruction of the 6-cell with associated decrease in insulin secretion) and an alteration in receptor-effector signal transduction (insulin receptor desensitization).

These new *allostatic states* are abnormal and generally pathological. Within this schema increased stresses (e.g. increased metabolic demands, infection, social and work obligations, etc) contribute to allostatic load which could favour the development of allostatic states, but only after offsetting, overriding and displacing the normal homeostatic processes, which includes rheostasis, that attempt to maintain a normal healthy balance.
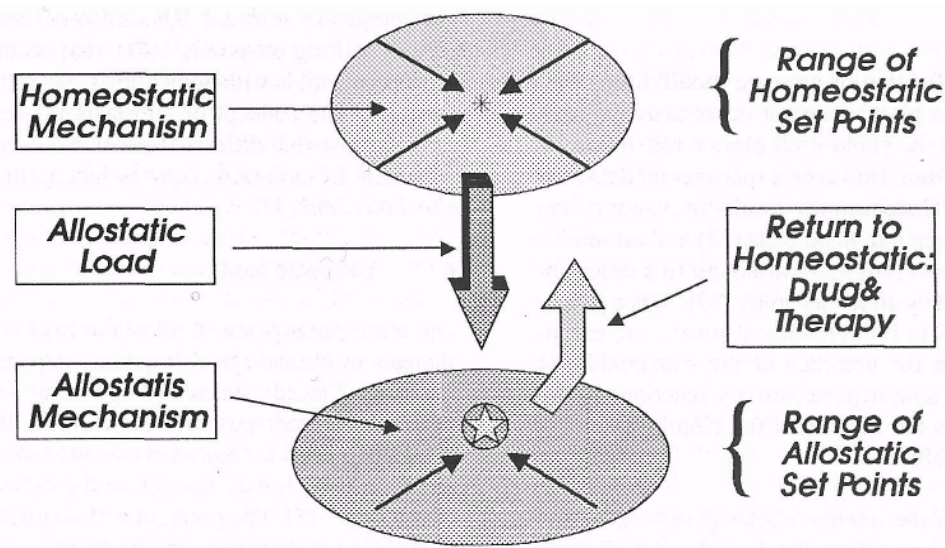
Figure 1. Homeostasis comprises the neural, endocrine and immunological mechanisms that maintain a physiological and biochemical parameter within a well defined range. The star in the middle represents an average set point or steady state. Under the influence of various stressors (allostatic load) the body may no longer be able to conserve a given parameter within the range manageable by homeostatic mechanisms. A pathology develops and an alternate state, that of allostasis, develops. It may be difficult, but not impossible, to return to the homeostatic state.

•   **Allostasis and diabetes mellitus**

The regulation of blood sugar levels is used to illustrate how the concepts of homeostasis, allostasis and allostatic load contribute to our understanding of the development of disease (Fig.2). Blood sugar levels are kept within a relatively narrow range, although fluctuations occur according to the time of day, age, exercise, and consumption of foods and drugs (46). These changes reflect the workings of normal homeostatic processes (the interactions of neuronal and endocrine systems) that modify set points in response to demands placed on the body. If, however, a stress, such as an inappropriate diet is imposed on the body, normal homeostatic mechanisms (e.g. glucocorticoids and insulin) may not be able to adequately control blood sugar levels. Allostatic load, such as excess production and release of insulin, reflects an attempt to correct the sugar imbalance. Even with these allostatic processes hyperglycaemia may persisit for extended periods of time, but if uncorrected a dysfunction in homeostasis may occur. This situation is not necessarily permanent provided that the corrective measures are taken to correct the imbalance (e.g. improved diet). However, with certain individuals this undue stress, especially if it is not corrected and if there exists concurrently a genetic predisposition to diabetes or obesity (another form of allostatic load), the onset of diabetes inevitably

ensues. The prediabetic individual can no longer maintain blood sugars adequately in the normal range by homeostatic mechanisms, and becomes an overt diabetic when blood sugar is controlled by other (i.e. allostatic) processes. Some of the allostatic processes used to control the hyperglycaemia are the deposition of fat, polyuria and polydipsia. Allostatic processes contributing to the pathology include insulin resistance and the shunting of glucose metabolism to the polyol pathway. The polyol metabolic pathway reduces the availability of phosphotidyl inositol required for normal functioning of the $Na\%K^+$-ATPase, and is believed to contribute to diabetic neuropathy (47).

The development of diabetes represents a shift from a homeostatic to allostatic state. The shift back to normal homeostatic control mechanisms is difficult, if not virtually impossible, and various long-term therapies must be initiated in order to control the pathology.

THE SALIVARY GLANDS: ROLE IN HOMEOSTATIC AND ALLOSTATIC PROCESSES

•   **Homeostatic regulation by salivary secretions**

Like most physiological variables salivary secretion is not con-
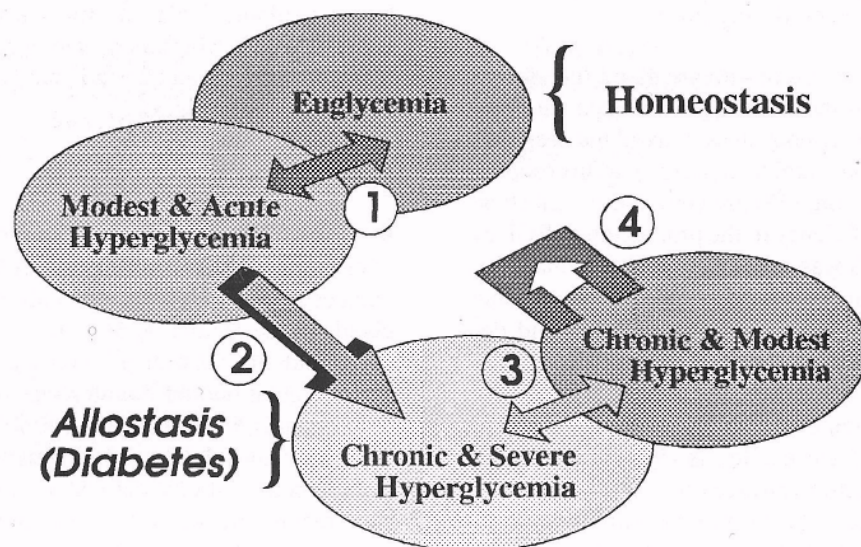
Figure 2. *Homeostatic and allostatic control is exemplified by considering control of blood glucose levels. Normal blood glucose takes on a range of values depending upon individual differences, age, diet, circadian rhythms and exercise, as is shown by the circle labelled euglycaemia. Under certain conditions the variations in blood sugar levels move outside this normal range, as occurs with the development of modest and acute hyperglycaemia. Although modest and acute hyperglycaernia is not normal,* **homeostatic mechanisms** *can still bring blood glucose back into the normal ranges (arrow 1). However, if under conditions of* **allostatic load** *(e.g. persistent hyperglycaemia and genetic predispositions) the individual becomes diabetic (arrow 2), and he/she then has moved into another state: one of allostasis. Diet management, insulin therapy and other drug treatments can correct, in part, the chronic and severe hyperglycaemia (arrow 3), but rarely is the individual able to achieve continued and permanent euglycaemia. The underlying pathology frequently prevents the return to homeostatic control (arrow 4).*

slant, but it is regulated by homeostatic processes to meet the changing demands imposed by environmental and sensory inputs. The sense of smell and the ingestion of food (9), as well as light (48) are key stimuli in eliciting salivary secretions. The increase of salivary secretions are needed during feeding to facilitate chewing and swallowing (7,49), and probably contributes to the maintenance of mucosal integrity during eating, as evidenced by increases in salivary EGF following mechanical stimulation of the oesophagus (50). Even under non-dietary demands salivary flow changes: keeping the mouth moist is essential for speaking. The salivary secretions of NGF and EGF also exhibit diurnal variation (51). Conditions of psychological stress, such as aggressive behavior, lead to an increase in circulating levels of NGF which derives from the salivary glands (52,53). The reason for this increase in circulating NGF is not known, but may be related to the adrenal gland hypertrophy that occurs with repeated fighting (52). Thus, salivary secretion is a dynamic process that is continuously modified to establish different and changing set points under the influence of specific demands.

- **Allostatic regulation of salivary secretion**

Salivary gland dysfunction, and concurrent xerostomia, is associated with a variety of connective tissue diseases identified with Sjo'gren's syndrome, such as rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, primary biliary cirrhosis and atrophic gastritis. Other conditions that manifest xerostomia are diabetes mellitus, cystic fibrosis, sarcoidosis, neurological disorders, and the graft-versus-host disease associated with bone marrow transplantation. For the majority of these disorders the xerostomia may be caused by the disease, although in certain cases a dysfunctional salivary gland could contribute to exacerbation of the disease.

- **The salivary glands and diabetes mellitus**

The allostatic model of physiological regulation proposed above suggests that if salivary secretion is dysfunctional then other physiological processes, which are inherently inappropriate for maintenance of normal function will become operative.

These compensatory changes may help maintain a functional organism, but in the long run they cannot respond appropriately to the demands placed on the organism.

A case in point is the alteration of salivary gland function in diabetes mellitus. Some of the pathology associated with diabetes may result from a deficiency in salivary gland secretion of EGF. Xerostomia and poor oral hygiene (54), reflux esophagitis and poor wound healing (55) are common in diabetics. An insulin correctable deficiency in the production of EGF by the submandibular glands was reported in diabetic mice (56, 57). The glandular dysfunction is associated with a chronic lymphocytic infiltration, glandular disorganization and destruction of the ductal cells, the source of salivary gland EGF (56). Although diabetes mellitus is identified with salivary gland dysfunction, their removal from diabetic rats results in a normalization of blood glucose levels (58). This antiglycaemia effect of sialadenectomy, which does not occur in non-diabetic rats, was attributed to the presence and release of extrapancreatic glucagon from the submandibular glands of the diabetic rats, and illustrates allostatic compensation by the salivary glands facing non-operative or dysfunctional homeostatic mechanisms.

• **Modulation of shock responses**

The importance of the submandibular glands in regulating homeostasis is further illustrated by the ability of these glands to determine the severity of shock responses to an endotoxic stimulus (38). Removal of the submandibular glands results in a more severe hypotensive response to intravenously administered endotoxin. Although the mechanisms responsible for this enhanced sensitivity to endotoxin have not been clearly established vascular reactivity to adrenergic neurotransmitters may be partly responsible (unpublished observations), and/or the ability of the neutrophils and macrophages to deal with the toxin may be modified (59,60).

The sensitization to endotoxin by sialadenectomy suggests that factors released from the submandibular glands modulate vascular and immune cell reactivity to inflammatory stimuli. These factors, acting as endocrine hormones, probably control the homeostatic mechanisms responsible for dealing with and responding to endotoxin and other inflammatory stimuli, such as antigen provocation of hypersensitivity reactions (37). Support for the notion that the submandibular glands regulate immunoregulatory homeostatic mechanisms was obtained when it was found that the effect of the removal of these glands on the severity of endotoxin-induced hypotension exhibited diurnal and circumannual variation (61). Sialadenectomy, by eliminating the source of immunomodulatory factors, removes inhibitory constraints that may prevent an excessive and harmnil reaction to circulating endotoxin. Upon removal of the sub-

mandibular glands one of the mechanisms responsible for homeostatic regulation of the responses to endotoxin is no longer available. Sialadenectomy is analogous to imposing an allostatic load, which is severe enough to move the animal into another state, an allostatic one, with its enhanced reactivity to endotoxin (Fig.3).

CONCLUSIONS

• By incorporating the concept of allostasis, which implies "another state" that is controlled differently from the homeostatic state, an understanding of the role of salivary glands in the regulation of body function is achievable. Salivary glands are consequently considered important participants in the regulation and maintenance of homeostasis. Dysfunctional glands, with a modified profile of exocrine and endocrine secretions, lead to marked perturbation of homeostasis. If these perturbations, defined as allostatic load, are of sufficient magnitude they lead to fundamental change in how the body responds to metabolic and environmental challenges. This modified state is an allostatic one. Further studies are required to evaluate salivary gland function in various diseases in order to determine the contribution that modified salivary gland secretions make to the development of specific pathologies. The profound impact of connective tissue diseases on the salivary glands suggests that this area of research should be quite productive.

ACKNOWLEDGEMENTS

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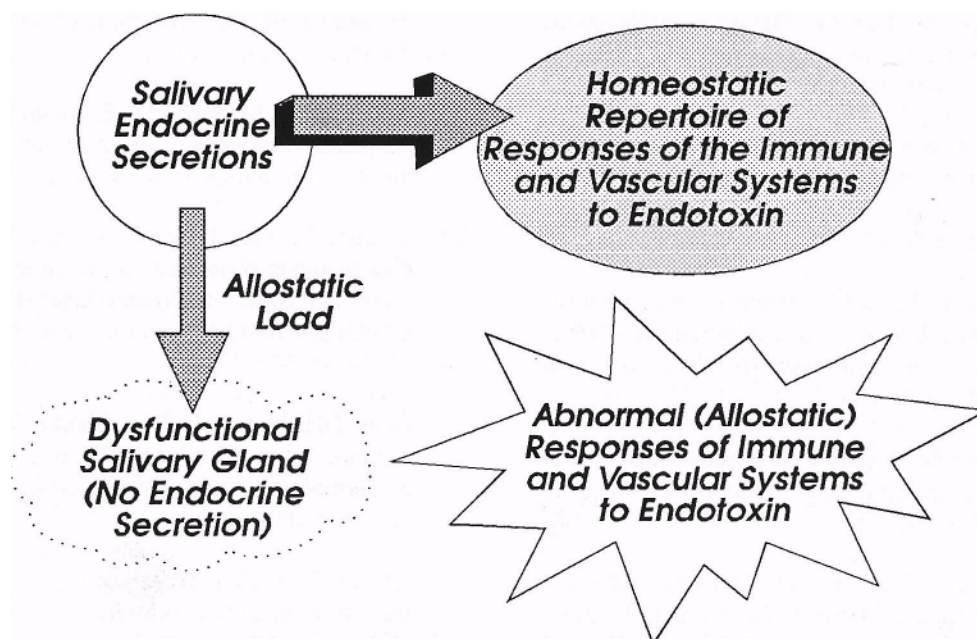
Figure 3. *Endocrine secretion of submandibular gland factors modulates the reactivity of the immune system, and help determine the variable homeostatic set points of immunoreactivity to endotoxin. If the glands are excised or become dysfunctional consequent to disease the secretion of these factors is abolished or reduced, and an inhibitory constraint imposed on the immune cells responding to endotoxin is removed. A new state of immune system responsiveness is induced which is different from the homeostatic state, and which cannot be regulated by the standard homeostatic mechanisms promoted by salivary glandpeptides. This new allostatic state is pathological in nature since the response to the endotoxin is exaggerated and the severity of the shock increases. The animal in an allostatic state cannot make the appropriate physiological adjustments required to maintain blood pressure imposed by the immunological insult.*

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