The structure and function of salivary glands

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Preface

Mastication and salivary secretion are crried out in the oral cavity. Foods are broken by masitcation, and the fractured foods are mixed with sailva. Saliva contains much water and α-amylase. This enzyme acts on starch and other complex carbohydrates, and decomposes them into dextrins, maltriose and maltose. In addition, the saliva has a lubricating property, and helps the tongue, oral mucosa, and teeth to function smoothly in speaking and swallowing. Thus, saliva plays an important role in maintaining digestion. The present report has been attempted to explain the outline of the structure and function of salivary glands.

1. The origination of the salivary glands.

Saliva is the general name for the secretory products from three major salivary glands and the small cavity glands such as libial, buccal, molar, palatal and lingual glands. These major salivary glands are composed of the parotid, submandibular and sublingual glands. The sali-vary glands are derived from both the ectoderm and endoderm in embryogeny[1]. The structure of salivary glands is more varied in vertebrates. For example, the development of human sali-vary glands occurs at about 5 weeks after pregnancy[2]. The submandibular glands which are one of the salivary glands begin to develop from 6 weeks[2,3]. The sublingual glands also begin to develop from 8 weeks. On the other hand, the parotid glands develop first, begin-ing at about 4 weeks[3] of intrauterine life and the differentiation to gland tissues occur after birth. Jocoby and Leeson[2] have described that in the rat submandibular glands the viviparity at about 16 days were observed the undifferentiated cells which had not only the secretory granules but peroxidase activity, and that the glands developed as a relatively discrete structure at about 19 days[2]. In addition, they describes that the terminal tubuls are regarded as the immature secretory unit in rat submandi-bular glands up to 6 weeks and that the gla-ndular acinis can be observed at birth. Changes in α-amylase activity in mouse parotid glands and pancreas were investigated during the embryonic and postanated development[4]. The amylase activity of mouse parotid glands in-creases from around 12 days and reaches the level of the adult at 30 days, whereas that of the pancreas arises during the last stage of pregnancy and, thereafter, progressively de-creases after birth[4]. The adult level of amylase activity is reached at 35 days old[4]. Futhermore, at birth the majority of human infants have negligible α-amylase activity in saliva. By 2 months the majority cf infants have appreciable levels of α-amylase and by 3 months several individuals reach to adult levels. However, a wide variation of saliva α-amylase levels bet-ween individuals is found for adults as well as for infants[5].

2. Histological and morphological obsarva-tions in the salivary glands.

Although mammalian species have three salivary glands, the parotid, submandibular

and sublingual glands, it seems that there is no significant difference between the submandibular and sublingual glands with respect to the functional or morphological properties. In these glands, the shape of the submandibular glands will be varied according to the difference of the species and sex. The weight of rat submandibular glands is about 200 mg, showing an elliptic shape. The glands exist under the mandible body. In dogs, its weight is about 5-10 g. The variety of submandibular glands including the sex difference is extended to the biochemical properties in spite of the distinction in the anatomical or histological components. Basically, the salivary gland is composed of the secretory terminals and the intralobular and extralobular ducts. The secretory terminals consist of many acinar cells. The acinar cells surround the lumen and their assemblages form the lobule. From the histological viewpoint, there are three Kinds of the salivary gland; that is, serous, mucous or mixed glands. These are classified by the difference in the dyeing to hematoxyline-eosin of acinar cells. This histological classification is not related to the secretory components. The parotid glands contain a number of serous cells. These cells contain the enzymatic granules(zymogen granules)and produce a watery secretion containing neutral carbohydrates and the digestive enzyme (α-amylase). The majority of acinar cells in the sublingual glands are mucous cells. The mucous cells secrete a viscous solution with mucopolysa-charides (e. g. sialic acid). On the other hand, the submandibular glands are composed of both serous and mucous cells. Therefore, the glands secrete both products. The amount of saliva secreted in humans is 1. 0-1.5 ℓ /day, and their saliva has the specific gravity 1. 002-1. 008 and pH 6. 4-6. 9.
Saliva contains a 99. 2 % water and most of the remaining substance (0. 73 %) containing the solid matters, such as compound protein binded to polysaccharides. In addition, it con-

tains salivary amylase, urea and non-proteinic nitrogen compound as organic compounds, and a good deal of Roden chloride primarily composed of chlorides and biocarbonates as inorganic compounds. The fact that much Roden chloride is contained in the saliva is a remarkable characteristic as compared with other body fluids. In particular, it seems that the saliva in heavy smoker contains much Roden chloride.

In the cell level study, no marked difference between the parotid and submandibular glands is observed in the structue of acinar cells. The number of secretory granules present within individual acinar cells somewhat varies. A large number of granules occupy the apical three-quarters of the cytoplasm, a smaller number of them interspersing between the rough endoplasmic reticulum cisternae.
The nuclei are generally located at the base of the acinar cells surrounded by abundant parallel arrays of the rough endoplasmic reticulum cisternae. In addition, a prominent Golgi complex is located apically, and/or laterally, to the nucleus. Immature secretory granules of varying sizes are presentin the Golgi region. Lysosomes and lipid droplets are occasionally observed. Lipid droplets tend to cluster at the base of the ell near then ucleus. The amount of lipid droplets seems to increase with age[6].

3. Nervous control of the salivary secretion.

The basal saliva is called the peculiar or resting saliva and is continuously secreted into mouth. Salivary secretion is activated by the psychic (e. g. gustation) and physical (e. g. mastication and swallowing) stimulations. All these activations are mediated by the reflex. The salivary secretory center exists in the medulla oblongate and its activation causes the excitation of sympathetic and parasympathetic nerve systems innervating the salivary glands. The salivary secretory center is composed of
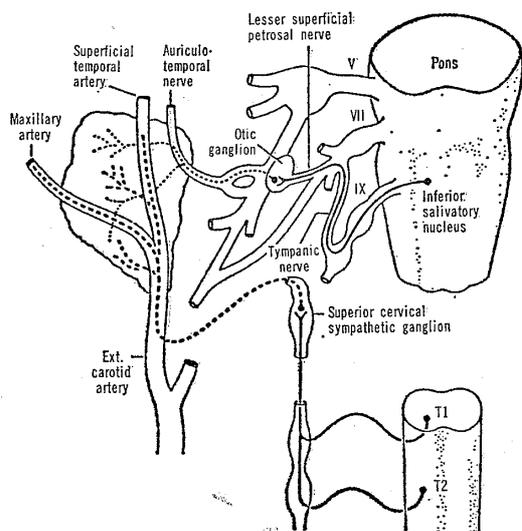
Fig. 1 Parotid gland : autonomic nerve supply. (by Mason, D. K., and Chisholm, D. M. : Salivary Glands in Health and Disease. Philadelphia, W. B. Saunders Company, 1975).

the two salivary nuclei in the medulla, as shown in Fig. 1. The flow rate and the property in salivary secretion are controlled by the autonomic nervous system supplied to the glands. The effects of autonomic nervous stimulation are mediated through each receptor in the acinar cells. In general, the stimulation of sympathetic nerve induces the secretion of saliva which has a viscosity and include more mucine. On the other hand, that of parasympathetic nerve induces the secretion of the water-soluble saliva containing much enzyme and inorganic compounds.

4. Regulative factors in the secretory process.

As described early, the salivary secretion is induced by the stmulation of both sympathetic and parasympathetic nerves. Besides, the secretion of saliva can be also elicited, at least in some species, by certain peptides, particularly some that are isolated from the skin of non-mammalian species or from the intestine or the brain of mamalian species, such as physalaemin, eledoisin and substance P[7-9].

Autonomic agents mimic the effects of electric stimulation in sympathetic and parasympathetic nerves (Fig. 2). The stimulating effects of these agents are mediated through the receptors, such as adrenergic (α and β) or muscarinic receptors. Adrenergic agonists, adrenaline, noradrenaline, phenylephrine and isoproternol, increase the salivary secretion by stimulating adrenergic receptors, whereas cholinergic agonists, acetylcholine, pilocarpine and carbachol, increase the secretion by stimulating muscarinic receptors. The stimulation of β-adrenergic receptors by adrenaline, noradrenaline or isoproterenol, causes the release of α-amylase and glycoproteins, and that of α-adrenergic receptors by adrenaline and phenylephrine causes the release of the electrolyte (potassium) from the salivary glands.

The increase in the activity of muscarinic receptors by cholinergic agonists induces the release of all secretory products.

This concept has been established from the finding that the effects of adrenergic and cholinergic agonists on the salivary secretion were inhibited by the addition of their selective antagonists, such as phentolamine, propranolol, metoprolol, and atropine.

It is now generally accepted that there are two distinict types of β-adrenergic receptors, termed "β_1 and β_2" by Lands et al[10].

Stimulation of adrenergic nerves in the rat parotid glands evokes the amylase secretion that is mediated *via* the activation of mainly β_1-type adrenergic receptors[11].

When Ca in the incubation medium is removed, the response to α-adrenergic and cholinergic agonists is considerably inhibited, but that to β-adrenergic agonists is not[12]. These events show that there is a difference between the action of α-adrenergic or cholinergic agonists and that of β-adrenergic agonists.

Furthermore, α-adrenergic and cholinergic agonists promote the Ca influx into the aicnar cells. This effect is also blocked by their antagonists. Therefore, it seems that Ca is one of key points in the secretory process. The im-
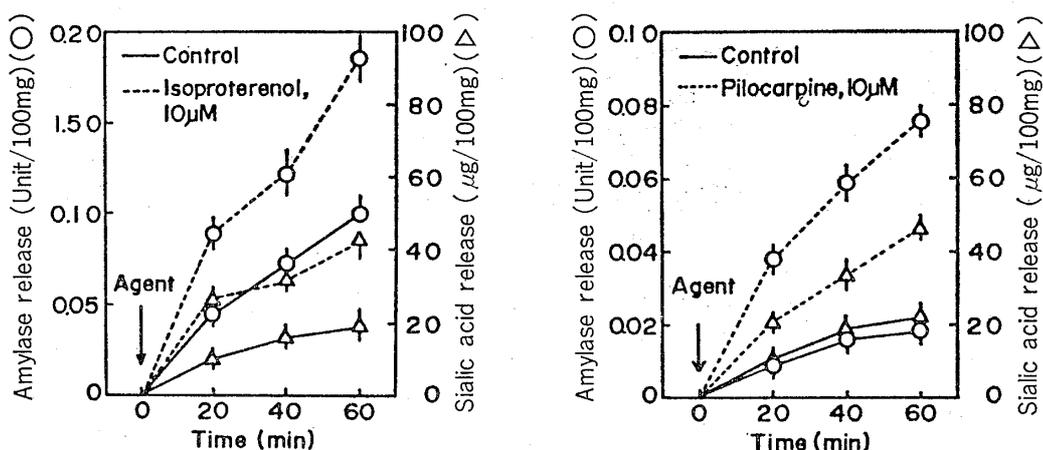
Fig. 2. Effects of sympathetic (isoproterenol) and parasympathetic (carbachol) agent
on the release of amylase and sialic acid in the dog submandibular gland slices.
(by Komabayashi, T. and Nakano, K.)

portance of Ca in various organs has been described by many laboratories. On the basis of these events, the term "stimulus-secretion coupling" was originally coined by Douglas and Rubin[13,14] to describe the sequence of events initiated by the acetylcholine stimulation of adrenal chromaffin cells and leading to the secretion of catecholamines by exocytosis.

They apparently had in mind the close similarity to the phenomenon of "excitation-contraction coupling" in muscle (namely, the key role of Ca in mediating both secretion and contraction the and parallel set of electrical and ionic events at the plasma membrane in response to acetylcholine).

A role of cyclic AMP in controlling salivary gland functions is noteworthy[15-17]. The salivary secretion due to the β-adrenergic agonist, isoproterenol, accompanies the increase in cyclic AMP accumulation.

This increase is significantly inhibited by the addition of propranolol. The utility of cyclic AMP is also recognized in the other endodrine and exocrine organs. The active manner of cyclic AMP in the secretory process is as follows. Cell metabolism is altered by the isoproterenol-stimulated activation of membranous adenylate cyclase, and the rise of cyclic AMP concentration subsequently triggers various control mechanisms through the

activation of cyclic AMP-dependent protein kinase[18] (Fig. 3).

The activity of adenylate cyclase is strongly affected, of course, by the excitation of β-receptors.

Following the discovery of calmodulin in 1970[19,20], a wide distribution of this Ca-binding protein has been demonstrated in several animals. Calmodulin is the acid protein of molcular weight 18,000 and can bind to four Ca ions. Calmodulin extensively is distributed in the pancreas, pituitary, brain, aorta and salivary glands.

However, the distribution in the salivary glands might be different between the species. Calmodulin has been found to mediate many of Ca effects in cellular functions[21]. A possibility is suggested that calmodulin plays an important role in the release of prolactin from pituitary gland and that of insulin and glucagon from pancreas. Recently, it has been reported that salivary secretion is dependent on calmodulin activity in dog submandibular glands[24].

5. Epilogue

In the present report, the author give an outline of the structure and secretory process of the salivary glands.
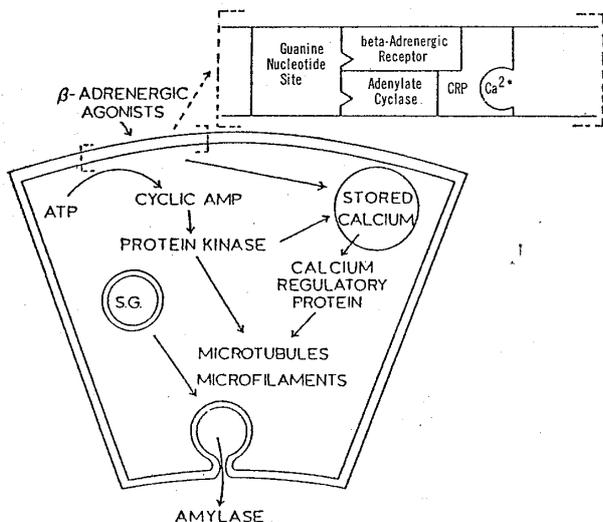
Fig. 3. Schematic diagram depicting various pathways to illustrate the possible interactions of Ca and Cyclic AMP in the regulation of amylase release. CRP, calcium regulatory protein, S. G., secretory granule. (by Butcher F. R. : Adv, Cyclic Nucleotide Res. 9, 707-721, 1978)

The study on the stimulus-secretion coupling advances year by year. Therefore, a number of theories will be promulgated to explain the secretory process.

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唾液腺の構造と機能

中野　慶子

食物は口腔内で唾液に混じ食道へ押しやられる。口腔に入った食物は反射的に分泌される分泌液と混じ，水分でうるおされ，こねられて固形性を失い食道，胃へと送り込まれる。唾液はさらに唇，舌の動きをなめらかにして口内と歯を清浄に保つ等の大切な働きを持っている。この様に食物が口腔内に入り，消化管で各栄養素にまで分解される過程において唾液の働きは第一関門といえる。我々の健康維持を目標とする栄養学的見地からも大変興味あることである。本報告は第1章から第4章で構成を行ない以下の通り要約する。

第1章　唾液腺発生について

唾液とは耳下腺，顎下腺，舌下腺から分泌されるものの一般的物質を総称したものであるが，これら3つの唾液腺の発生は頬部上皮から発生するものと考えられている。脊椎動物における唾液腺の構造は多種多様であり，その多様性の発生は系統発生と共に変動的である。哺乳動物における唾液腺の個体発生についてはヒトでは胎生の5週頃から始まり大唾液腺のいずれも内胚葉ならびに外胚葉から由来するものとみられる。そして出生後に腺組織へ分化し完成していく。

第2章　唾液腺における形態学的組織学的観察

唾液腺を形態学的，組織学的にみると acinar cells が直接の前駆体であると考えられているが，多くの哺乳動物の唾液腺の性状は腺房部細胞の hematoxyline-eosin に対する染色性の違いから分類されており，それにより粘液腺，漿液腺，混合腺の3つに分類される。これは分泌部に漿液物に富む細胞と粘液物に富む細胞の区別による。しかしこの様な分類は組織学上行なわれているものでその内容物と関係したものではない。多くの哺乳動物の舌下腺と耳下腺では機能的にも形態学的にも種差は少ないとされており，舌下腺はムチンに富み消化酸素の分泌も少量である。また，ヒトやラットを始め多くの動物の耳下腺は主として消化酵素であるアミラーゼの産生，分泌を行なう。アミラーゼは顎下腺にも含まれるけれどもその含量は一般に耳下腺より少ない。

第3章　唾液分泌の神経的調節

唾液分泌の機序における神経調節は口腔内に食物が入ると反射的に唾液が分泌されるが，これは唾液腺を支配している交感神経と副交感神経の興奮によって行なわれる（Fig. I.）すなわち消化管と同様に自律神経の2重支配を受けているのであるが，両神経とも分泌を促進する。交感神経は粘稠性の高い唾液を，副交感神経は粘稠性の低い，水溶性の唾液を分泌させる。

第4章　唾液分泌における調節因子

唾液の分泌は自律神経系を電気刺激すると増加するが，この効果は交感神経終末からのノルアドレナリンならびに副交感神経末端からのアセチルコリンの放出によって起ると考えられている。この様なことから，外因的にアドレナリン作動薬やコリン作動薬を適用しても唾液分泌の亢進が起る。最近の研究からフェサラミン，エレドイシン，サブスタンスPなどのポリペプタイドも唾液分泌を増加させることが報告されている。これらの唾液分泌の亢進はそれぞれのレセプターを介して惹起する。また，分泌機構にカルシウムの関与が示唆されカルシウムが重要な役割りを持っていることが色々な器管においても数多く報告されている。カルシウムを溶媒中から除去した場合はアドレナリン作動性およびコリン作動性腺維はその反応を著しく抑制される。このことから唾液分泌過程にカルシウムが重要な関わりを持っているものと考えられている。更に唾液分泌機構における Cyclic AMP の役割りは広く知られていることである。カルシウム受容蛋白質であるカルモデュリンについても細胞内での分泌機構で重要修飾因子であることが報告されている。この蛋白質は唾液腺の他に膵臓，下垂体，脳，大動脈等に広く分布している。この様に今日までの報告について検討を加えたが，近年刺激一分泌連関機構に関する研究はますます盛んになる一方である。これら以外に重要な因子となる物質も見出され，詳細な分泌機構が明らかになるものと思われる。