

GENERAL CONSIDERATIONS

Since more than a century it has been shown by a number of scientists that the secretion of saliva is controlled by both the branches of the autonomic nervous system (Langley, 1878; Carlson et al., 1907; Kesztyus and Martin, 1937). Although stimulation of either branch would result in increased salivation, the composition of the secretion would depend on the branch stimulated. A concept has been developing over later years that the autonomic nervous system plays significant role in maintenance of functional as well as structural status of the salivary glands.

At the levels of microscopic structure and cellular functions the duct system of salivary glands has been linked to that of renal tubules so far as secretory/absorptive functions are concerned; down the duct system. In other words, as with nephric tubules, the primary fluid entering the ducts undergoes serial and orderly modifications, particularly with respect to concentration of electrolytes and water content. The primary salivary fluid is a product of secretory activity of the acinar cells. Here the larger molecular species secreted, like enzymic proteins and highly polymerized glycoproteinous compounds, are not amenable to removal of absorptive processes.

Yet another aspect about the structure as well as functions of the mammalian salivary glands was brought to light by the pioneering work of Lacassagne and associates (1940 to 1970) on sex-related differences demonstrable in laboratory mice. Later,

on the basis of reports on mice, rats and several other mammals, including human beings, it was realized that the differences are not just sex-related but sex-dependent, and further, that this glandular apparatus exhibits sensitivity to variations in the levels of sex hormones.

The present work was mainly based on the following premises:-

- a) If sex-dependent influence is there, then naturally this should be effected through enzymic systems concerned with, if not all, at least some of the major patterns of metabolism.
- b) In such context, generally the methods of universal choice are experimental deprivation and subsequent replacement therapies. Normally, with reference to other endocrinological effects in case of other sex-dependent tissues and glands due to surgical ablation of gonads have been studied after considerably longer post-operative intervals. It appeared to the author that this possibly would not be applicable to at least the salivary glands, particularly considering the sustained pattern of functioning of these glands. Moreover, during the recent years it has been amply proved that the half-life of circulating sex-hormones is a matter of only few minutes to a few hours. It was thus deemed worthwhile to investigate the rapid effects of sex hormones on some aspects of metabolism of salivary glands of young mature male albino rats. Additionally, it was also thought necessary to study the effects of exogenous administration of androgen as well as that of estrogen to intact male rats; for gaining a wider and comparative base for understanding the effects due to castration and hormone replacement.

c) As cited at the beginning, the autonomic nerves are necessary for normal structural and functional integrity of salivary glands. It had become obvious, during the course of exploratory work, that the β -adrenergic functions apparently regulate preferentially the metabolic processes of glandular tissues rather than the mechanisms of release of salivary fluid. It, was, therefore, thought desirable to know more about the influence of adrenergic drugs on the similar aspects of metabolism apparently not assessed hitherto.

d) Generally, the exposed epithelial surfaces of the body are normally covered with mucinous substances as a measure of overall protection. Oral cavity is also copiously provided towards this purpose with saliva. An important biochemical basic component of such mucinous covering is the class of sialic acid polymers. Reasonably enough, then, information on sialic acid content and alterations thereof due to experimental manipulations of steroid hormones as well as due to administration of adrenergic drugs, would be of interest.

Therefore, as stated earlier, the plan of present investigation was drawn up to look into the aspects spelled out above. Emphasis was naturally on rapid effects of hormone deprivation, replacement therapy and drug administration.

Sexual dimorphism of the salivary glands of mice and rats has long been demonstrated and that administration of sex hormones was shown to lead to morphological changes in the salivary glands.

Later, the androgenic influence on the rodent salivary glands has been confirmed on the basis of enzymic and histochemical studies by several workers (Chaulin-Serviniere, 1942; Raynaud, 1950; Cassano 1958; Ferguson et al., 1970; Katkov et al., 1972). Berkman and Kronman (1970) reported that only the submandibular glands are sensitive to alterations in the androgenic levels but not the sublingual and parotid.

Observations presented in this work also brought up supportive evidence in that the cholesterol content of submandibular gland is also sensitive to variations of androgenic titres. It was found that castration (48 hr) led to its accumulation and that it could be restored to normalcy with TP replacement. The present study being confined to only short term effects transitory fluctuations were seen, which were not always found to agree with previously reported long term (a few weeks) effects the latter being perhaps stabilized by then. In case of total lipid content of the gland gonadectomy was seen to lead to its reduction and TP administration could correct it back. However, the variation in the glandular lipid content were more or less steady, as compared to those of cholesterol (Chapter I). Long term effects of castration have been reported to reduce ascorbic acid content in various tissues (Chinoy et al., 1979). Paradoxically, an increase was obtained here in the glandular AA content due to castration and subsequently its restoration due to TP administration, at least upto an hour. This probably indicated a regulatory role for androgens as far as AA requiring metabolic reactions of submandibular gland are concerned

(Chapter I). Observations reported in Chapter VI concerning the influence of exogenous administration of TP to intact male rats revealed an enhancement of total lipid, cholesterol and AA content of the gland. This was possibly due to enlargement of granular tubules, as has been already reported by Kronman and Spinale (1965) under androgenic influence. However, the present author likes to add here that there should have been replacement at functional level too, of this important part of the gland. The study of castration and replacement with TP revealed a rise in the glycogen content of the gland alongwith variations in the concerned enzymes (Chapter II). Observed increase in the glycogen content due to castration is well in agreement with the observations of Sreedeviamma and Oommen (1987) and Ambadkar and Gangaramani (1982). A depletion in aldolase and SDH enzyme activities implies that the glycolytic pathway as well as oxidative breakdown of carbohydrate was on a low key (Chapter II). Replacement with TP was seen to restore the observed changes due to castration. However, restoring capacity was just transitory. Thus, it could be suggested that 100 µg TP dose is not enough to bring about sustained normalcy in the enzyme activities as well as the contents of metabolites. Secondly, to understand such short-term effects further work is necessary before arriving at any conclusion.

Exogenous administration of TP was observed to increase glandular glycogen alongwith increase in glycogen synthetase activity and decrease in phosphorylase activity (Chapter VI). Again, this effect was seen upto an hour of TP administration. The membrane

bound $\text{Na}^+\text{-K}^+$ -ATPase activity was influenced only at a later time interval of 2 hr. It could be inferred from this that the hormonal effect on various metabolites could possibly be brought about via the mediation of c.AMP, because PDE activity was found to alter under these experimental conditions (Chapter II and VI).

Orchidectomy was found to reduce the total sialic acid (SA) content and replacement could slightly recover it and that too, transitorily (Chapter VII). It could be suggested that a certain critical balance of androgens must exist that regulates mandibular SA content in male rats. This holds as far as short-term effects are considered. Such depleted levels of SA content would naturally lead to secretion of more watery saliva.

The overall effects of administration of 17β -estradiol on submandibular glands of male rats were more or less similar to those obtained after TP administration (Chapter VII). The author here is tempted to presume that TP as well as estradiol- 17β , in all probability, were converted to some particular metabolite by enzymic machinery of the submandibular glands of male rats, and that the latter in its turn activates a common pathways of metabolism.

Various experiments carried out by different research workers elucidate further the influence of adrenergic as well as cholinergic agents on the patterns of secretion of saliva and functioning of the glands (Schneyer et al., 1983; Jirakulsomchok et al., 1984; Schneyer and Jia-Huey, 1984). The present investigation, by

administering isoproterenol (IPR) and propranolol (PPN) and by employing biochemical methods, has clearly revealed that the rat submandibular gland is controlled through β -adrenergic receptors and that this effect is blocked by β -adrenergic antagonist (Chapter III, IV and V). The total lipid as well as cholesterol content was found to decrease under IPR influence and increase under PPN administration. Similar decrease in lipids in other tissues due to IPR administration has been reported (Weiss et al., 1980; Correze et al., 1982; Gaben et al., 1984).

Glycogen content was found to have decreased due to IPR administration and the same was increased after PPN administration. The adrenergic agonist and antagonist were observed to be less effective at the mitochondrial level as the SDH activity did not exhibit noticeable alteration (Chapter IV and V). Whatsoever be the mechanism underlying the influence of these two drugs; it could be said at present that the agonist and antagonist effect on β -adrenergic receptors noticeably influences the glycogen, lipid, cholesterol and ascorbic acid metabolism in the submandibular gland at such early interval, initially directly and later probably through mediation of intracellular c.AMP.

It was clearly seen that β -adrenoreceptors do play a role in the regulation of glandular SA content of male rats in a significant manner. IPR administration was found to lower SA within 60 min and PPN removed this suppressing effect thereby significantly increasing the SA content.

From the present study it is difficult to judge as to whether the adrenergic receptors are influenced by sex steroid levels or the androgens affect the metabolic patterns of the gland directly (Minetti et al., 1985). Though the precise mechanism of adrenergic as well as steroid regulation is not known at this stage, the present findings open up new vistas for further studies on factors controlling metabolic patterns in the submandibular glands of male albino rats. This would be of importance not only for researchers but also to pathologists and clinicians, owing to pharmacological implications of such influences.