

Role of Autonomic Pathways in Disuse Atrophy of Rat Parotid (37244)

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Previous work has shown that parotid size can be effectively reduced by surgical elimination of either or both branches of the autonomic nervous system (1, 2) or by the disuse atrophy resulting from maintenance of animals on an all-liquid diet (3-6). With denervation, activity-mediated (impulse) as well as trophic (nonimpulse) influences of the autonomic pathways are eliminated. With liquid diet (Metrecal), since the innervation remains intact, trophic effects of the innervation remain and only activity-mediated effects of the innervation can be assumed to be involved in the glandular atrophy resulting from disuse. It has not been determined, however, whether neurally mediated glandular activity is only reduced, or is completely eliminated with Metrecal. Furthermore, the extent to which each branch of the innervation is involved in Metrecal-induced atrophy has not been ascertained. The present work was undertaken to determine how Metrecal causes glandular atrophy and to what extent each of the autonomic pathways is involved in the production of the atrophy. To this end, liquid diet was used in conjunction with selective and complete denervation. Analysis of the data provided some insight into the respective activity and trophic effects of each branch of the innervation.

Materials and Methods. Four-month old, isogenic Fischer strain rats were selected for denervation. The operations were performed under ether anesthesia. Postganglionic parasympathectomy (Px) was achieved by removal of a 5 to 10 mm section of the ipsilateral auriculotemporal nerve. Postganglionic sympathectomy (Sx) was achieved by removal of the ipsilateral superior cervical ganglion. A sham operation was performed on the opposite side after denervation.

The animals were allowed to recover for 2 wk on a solid chow ration before beginning an experimental ration of either solid chow and tap water or liquid Metrecal, given *ad libitum*, for an additional 2 wk. Liquid Metrecal was prepared and dispensed daily as described previously (3). Water was dispensed in the same type of container as used for the Metrecal. Atropine SO₄ (1.5 mg) was given as an intraperitoneal injection to some rats every 3 hr for a total of 3 injections each day. These atropinized rats were fed, *ad libitum*, either Metrecal or chow only during the 9 hr period of expected drug action. Prior to sacrifice, rats were fasted for 24 hr with water available. Under seconal anesthesia (5 mg/100 g body wt), rats were exsanguinated by cardiac puncture. The parotid glands were dissected free of fat, lymph nodes, and muscle and immediately weighed on a torsion balance.

Results and Discussion. Comparison of parotid weight of rats maintained on solid chow with that of rats maintained for 2 wk on a liquid diet of Metrecal revealed that gland weight of Metrecal-fed rats was 33% less than that of chow-fed rats (Table I). The weight reduction with Metrecal was considerably less than that effected by complete postganglionic denervation (PxSx), for gland weight in rats fed either Metrecal or solid diet was reduced by 50%. Thus, all autonomically mediated influences are not eliminated with liquid diet only and the approximate 17% difference between parotid weight of normally innervated glands of Metrecal-fed rats and PXSx glands, represents a residual, autonomically mediated influence in the Metrecal-fed rats.

This residual influence appears to be parasympathetic. This is clear from the following

TABLE I. Effects of Interruption of Efferent Nerves on Parotid Gland Weight of Rats Fed Metrecal or Chow.

Condition	No. rats	Ration	Parotid gland wt (mg)	Decrease (%) from intact chow control	Final body wt (g)
Intact	10	C	111 ± 5 ^a	—	151
	8	M	74 ± 2	33	161
Intact and atropine ^b	9	C	74 ± 5	33	117
	10	M	58 ± 2	48	129
Sx ^c	10	C	96 ± 5	14	152
	10	M	73 ± 3	34	154
Px ^d	12	C	69 ± 3	38	150
	8	M	54 ± 3	51	147
PxSx	6	C	57 ± 4	49	148
	8	M	54 ± 5	51	164

^a Mean ± SE.

^b Atropine SO₄ 1.5 mg ip 3 × daily; rats fed only during period of drug action.

^c Postganglionic sympathectomy.

^d Postganglionic parasympathectomy.

comparison. When glands of Metrecal-fed rats were parasympathectomized, the residual autonomic influence observed with Metrecal alone appeared to be eliminated since a maximal reduction (about 50%) in gland weight was effected (Table I). The data also suggest that the sympathetic branch is not involved in this residual autonomic influence. First, the same reduction in weight (50%) occurred in PxSx glands as in Px glands of Metrecal-fed rats; and second, weight of Sx and normally innervated glands of Metrecal-fed rats did not differ from each other (Table I). Finally, it is clear that no additional efferent pathways can be implicated in accounting for this residuum, since PxSx glands of chow-fed rats showed the same maximal reduction in gland weight exhibited by PxSx glands of Metrecal-fed rats.

The nature of this residual parasympathetic influence is not unequivocally established by the present data. This parasympathetic influence may be trophic or may represent residual activity. Recent evidence suggests it may be trophic. When pairs of submaxillary glands are removed, a marked increase occurs in the gland size of the remaining parotid (7) as a consequence of compensatory activity; if animals, however, are maintained on a liquid diet, the compensatory enlarge-

ment does not occur (8). This finding suggests that with liquid diet, all neurally mediated activity is eliminated and not simply reduced, and therefore any remaining parasympathetic influence must be trophic. On the other hand, the possibility that the residual autonomic influence is activity-mediated is suggested by the finding that administration of the cholinergic blocking agent, atropine, to Metrecal-fed rats resulted in the same maximal degree of atrophy obtained in the PxSx glands. This suggests that cholinergic receptor activity was not completely eliminated by the diet. However, the evidence in support of this thesis is weakened by the observation that atropinized rats lost weight during the drug treatment. This loss of weight was probably not the result of decreased length of time of food availability, since not only weight loss, but the occurrence of scruffy coat and listless behavior suggested that the rats were ill. Until it is established that organ weight was not a reflection of the concurrent body weight changes, this argument is not adequate. Thus, the data are at least suggestive of the possibility that residual parasympathetic influence on parotid is a trophic effect. Furthermore, since parasympathectomy has been shown to decrease cell number as well as cell size (9), whereas

liquid diet reduces cell size only (6), this possible trophic effect may be important in maintaining cell number.

While the sympathetic pathway is not involved in the residual autonomic influence present with Metrecal, it does play a role in Metrecal-induced atrophy. Thus, Px glands of chow-fed rats, where the sympathetic innervation is intact and active, were greater in weight than Px glands of Metrecal-fed rats where the sympathetic innervation is also intact, but presumably inactive (Table I). This 13% greater reduction in gland weight with Metrecal was comparable to the 14% reduction observed when the sympathetic fibers to the parotid in chow-fed rats were surgically removed. These influences of the sympathetics in Metrecal-induced atrophy involve only activity-mediated effects, since trophic influences of this branch are not evident. This is clear from the data in Table I. Sympathectomy of either intact or Px glands of Metrecal-fed rats did not further reduce parotid weight. In addition to these data obtained with surgical denervation, further confirmation of the role of the sympathetics in Metrecal-induced glandular atrophy was obtained from experiments involving chemical denervation. When atropine, an agent which blocks cholinergic activity, was administered to rats fed liquid diet, the decrease in gland weight was greater than that observed in atropinized rats fed chow. The magnitude of this difference (15% of chow control) was equivalent to that obtained by surgical denervation (13% of chow control). These data thus provide substantial evidence for the role of the sympathetic innervation in Metrecal-induced atrophy of the parotid gland. Furthermore, this role of the sympathetics involves only activity.

The role of the parasympathetic innervation in Metrecal-induced atrophy is even more prominent than that of the sympathetic. When compared with normally-innervated glands of rats fed chow, Sx glands of chow-fed rats were 20% larger than Sx glands of Metrecal-fed rats (Table I). This represents the parasympathetic influence in Metrecal-induced atrophy. Further support for this specific contribution of each branch of the

innervation in Metrecal-induced atrophy is based on the observation that the weight reduction with Metrecal is about equal to the sum (33%) of the weight reduction caused by liquid diet and mediated by the sympathetic (13%) and parasympathetic (20%) innervations. Finally, it may be mentioned that these effects are observed not only with the particular liquid diet Metrecal, but are also demonstrated when other liquid diets (3, 5, 9) are used instead.

Liquid diet remains an effective means for reducing neurally mediated activity, but it is clear that all autonomically mediated influence, whether activity or trophic, is not eliminated by such a regimen. Although denervation eliminates both activity and trophic effects, it has other disadvantages. Denervation, *e.g.*, characteristically results in a degeneration secretion and supersensitivity. Thus, liquid diet is the more convenient and better tool for reducing the level of parotid activity.

Summary. Selective section of the auriculo-temporal nerve and removal of the superior cervical ganglion in rats fed Metrecal or chow resulted in differing degrees of parotid weight reduction. The maximum reduction (50%) in weight occurred with PxSx glands of rats fed Metrecal or chow and with Px glands of rats fed Metrecal. The weight reduction in normally innervated glands of rats fed Metrecal was about 17% less than this maximal reduction. This residual autonomic influence was found to be mediated by the parasympathetic innervation and may represent a trophic effect. The sympathetic innervation, nonetheless, played a role in mediating effects of activity on parotid size. About 13% of the 33% reduction in parotid weight (disuse atrophy) induced by liquid diet was attributed to the sympathetic innervation and about 20% to the parasympathetic innervation. In view of the altered physiological status of the gland with surgical denervation, liquid diet remains a more effective and convenient means of producing disuse atrophy of parotid gland than denervation.

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