DYNAMICS OF POSTDENERVATION DISTURBANCES OF HUMAN PAROTID SALIVARY GLAND FUNCTION

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After denervation of a skeletal muscle, dispersion of nicotinic acetylcholine receptors is known to take place over the whole surface of the extrasynaptic muscle membrane, which leads to an increase in sensitivity of the muscle fibers to neurochemical stimuli. Conversely, reinnervation of the muscle leads to concentration of nicotinic (N) acetylcholine receptors in the zone of synapses, with a decrease in sensitivity to mediator action [1, 5-7]. The question whether similar relationships exist in the case of denervation of the salivary gland has not been adequately investigated. In the writer's study of 110 patients denervation of a salivary gland occurred after head injury and operation in the region of the tympanic cavity, with division of the tympanic nerve and its branches. Some general principles common to both N and muscarinic (M) acetylcholine receptors were revealed.

During the last year, all manifestations of the postdenervation syndrome have been accurately monitored under in-patient, and later under out-patient conditions. Since, in the writer's opinion, these investigations are of great interest, one typical case will be described in detail below.

EXPERIMENTAL METHOD

Patient S., a man aged 33 years, was admitted to the Neurosurgical Department on February 16, 1981, after falling from a height of 1-2 m. He had lost consciousness for a short time, was somewhat confused, was bleeding from the left ear, and had blood-stained CSF. Cranial roentgenograms revealed a longitudinal crack in the left temporal bone, crossing to the petrous portion of the temporal bone. A full investigation required determination of involvement of the tympanic nerve and its plexus (Jacobson's plexus). Since the tympanic nerve controls parotid salivary gland function, the following parameters were studied in this patient by the usual method [2-4] (using Lashley–Krasnogorskii capsules) bilaterally: spontaneous salivation; reflex secretion in response to unconditioned stimulation (0.5% citric acid) for 3 min during its action and in the after-period; secretion in response to subcutaneous injection of 0.4-0.5 ml of 1% pilocarpine; saliva secretion in response to subcutaneous injection of a mixture of 0.5 ml pilocarpine and 0.5 ml of 0.1% atropine; salivation in response to subcutaneous injection of 0.6 ml of 1% atropine; secretion in response to subcutaneous injection of 1 ml of 0.05% neostigmine.

EXPERIMENTAL RESULTS

The results are given in Table 1 in chronological order, for a definite sequence of disturbances was discovered.

A. Initial Stage of the Denervation Syndrome. Responses of the gland observed before appearance of a paradoxical cholinomimetic response to cholinolytics were described as belonging to the early stage of denervation. It will be clear from Table 1 that in this period spontaneous secretion decreased in the absence of reflex salivation, and the response to pilocarpine was increased by 100%; atropine under these circumstances did not induce a paradoxical effect and inhibited the action of pilocarpine injected at the same time and mixed with it.

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TABLE 1

Spontaneous secretion in 3 min			Reflex secretion in 5 min			Pilocarpine secretion in 60 min				Secretion in response to injection of 0.5 ml atropine and 0.5 ml pilocarpine				Secretion in response to injection of 0.6 ml atropine				Remarks
date	D	C	date	D	C	date	dose	D	C	date	duration of observation, min	beginning of paradox	D	C	date	duration of observation, min	beginning of paradox	D	C	
10/III	0,05	0,3																		
16/III	0,0	0,8	16/III	0,0	1,5	11/III	0,4	15,0	7,4	10/III	45 min	—	7,5	1,6						
25/III	0,0	0,3													20/III					
30/III	0,0	0,4								13/III	60	—	12,4	—		160	24	115,2	4,5	
3/IV	0,1	0,6								16/III	205	60	160,8	5,0						Induction at 60 min
7/IV	0,1	0,6	7/IV	0,7	3,2					25/III	170	21	142,8	8,8	30/III	150	18	137,2	9,6	
13/IV	0,2	0,6	3/IV	0,7	1,5					7/IV	170	23	150,3	12,2	3/IV	120		44,3	5,3	
15/IV	0,2	0,4				15/IV	0,4	23,0	16,0											
17/IV	0,3	0,6								17/IV	180	25	155,2	11,2						
21/IV	0,2	0,5	4/V	1,2	2,6					28/IV	170	22	147,0	14,8						
15/V	0,4	0,8	15/V	2,2	3,0	15/V	0,5	23,6	21,2	11/V	120		38,0	0,8						Secretion in response to 0.05% neostigmine in 60 min
19/V	0,4	0,8								19/V	120		42,4	12,0						
22/V	0,4	0,4													22/V	120	Induction at 30 min	72,6	1,6	
27/V	0,3	0,4													27/V	100		40,5	1,6	
5/VI	0,4	0,6	23/VI	2,4	1,8										5/VI	60		5,0	2,6	
16/IV	0,5	0,5								16/VI	105		6,0							26/VI
25/VI	0,4	0,2				1/VII	0,5	18,8	15,8						23/VI	130		13,8	5/0	D 11,5 C 8,8

Legend. All tests carried out in 1981. D and C) Denervated and control glands respectively.

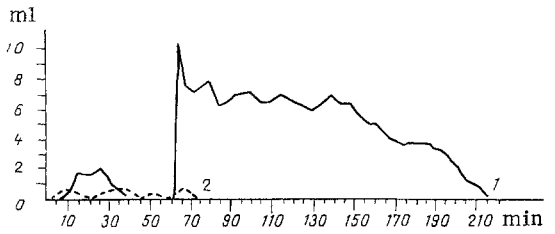

Fig. 1. Latent (inducible) form of atropine paradox (March 16, 1981). 0.5 ml of 0.1% atropine and 0.5 ml of 1% pilocarpine injected subcutaneously. Before induction (at 60th minute) 9 ml saliva was secreted from the denervated (1) gland and 4.8 ml from the control (2) gland in response to pilocarpine. During first 5 min after induction (0.5% citric acid) 10.5 ml of saliva was secreted ("explosive" type from the denervated gland and 0.7 ml from the control gland. In response to atropine 160.8 ml saliva was secreted from the denervated gland and 5.0 ml from the control gland. Here and in Fig. 2: abscissa, time (in min); ordinate, secretion (in ml).

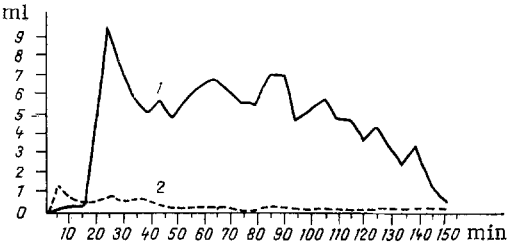

Fig. 2. Overt form of atropine paradox (March 30, 1981). 0.6 ml of 0.1% atropine injected subcutaneously. During first 5 min (from 18 to 23rd minutes) 13.0 ml saliva was secreted. Total saliva secreted during period 12-150 min 137.7 ml from denervated gland (1) and 9.6 ml from control (2).

B. Late Stage of the Denervation Syndrome. This stage is characterized by the appearance of an extremely intensive and prolonged response, of high amplitude and repeatable, to small and normal doses of atropine. Initially to reveal the paradoxical effect in response to atropine, special stimulation (induction) of this effect was necessary, for which purpose very weak acid food stimulation of the oral mucosa was applied against the background of atropinization (Fig. 1). By this method it was possible to discover a latent form of atropine paradox, which in many subjects does not progress to the overt form, when the salivatory effect of atropine arises spontaneously, without additional stimulation. In our patient the induced paradoxical response to atropine preceded the appearance of the overt form of the paradox, which continued persistently for 10 weeks (Table 1; Fig. 2).

C. Recovery Stage of Postdenervation Syndrome. During this period gradual recovery of both spontaneous and reflex secretion was observed on the side of denervation, and later these effects were stronger than those in the control gland.

The increase of 100% in pilocarpine secretion observed in this patient in the initial stage subsequently fell to 44-17% (Fig. 3). The paradoxical salivatory response to atropine

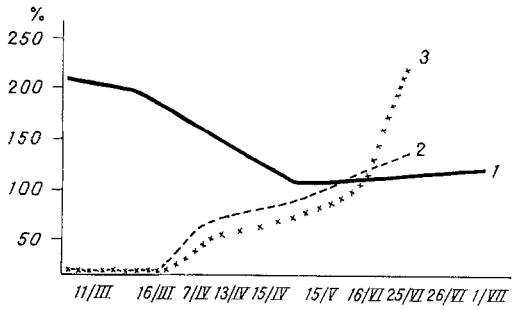

Fig. 3. Time course of spontaneous and pilocarpine-induced (1) and reflex (2) secretion in different phases of postdenervation period. Curves of pilocarpine and reflex effects and also of spontaneous salivation intersect. Ordinate, volume of saliva secreted (in % of control); abscissa, day and month.

also became smaller and it ceased more rapidly. At the end of the period of observation the overt form of the paradox disappeared and only its latent form was manifested. This form then also disappeared, so that the complete cycle of events was thus reversed.

All stages of the postdenervation syndrome in the human parotid salivary gland after division of the secretory nerve were thus monitored under both in- and out-patient conditions. Three consecutive stages of reorganization of gland functions were distinguished: 1) an initial mild stage with loss of unconditioned secretion and with increased sensitivity to cholinomimetics; 2) a more severe stage with reversal of the response to cholinomimetcs, i.e., with the appearance of extremely intensive salivation in response to atropine, and 3) a recovery stage, with gradual restoration of spontaneous and reflex secretion, depression of the increased sensitivity to cholinomimetics, and abolition of the atropine salivatory paradox.

During transition from the early, initial stage to the more severe, late stage, and also during restitution, i.e., transition from the severe stage to the recovery stage, a special, inducible state of functions of the gland was discovered, when the paradoxical effect to atropine could be evoked only by additional unconditioned-reflex stimulation of the oral mucosa.

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