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TRANSFORMATION OF THE CHOLINOLYTIC EFFECT OF ATROPINE ON THE DENERVATED HUMAN SALIVARY GLAND INTO CHOLINOMIMETIC DURING REFLEX STIMULATION*

S. L. Levin

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In previous communications an atropine salivatory paradox was described, namely extremely intensive secretion of saliva, high in amplitude, steady and protracted, in response to small and ordinary doses of atropine by the denervated human parotid salivary gland, reproducible for many years [1, 2]. Denervation occurred after trauma to the base of the skull, a fracture of the petrous part of the temporal bone, and operations and pathological processes in the zone of the tympanic cavity. Disappearance of unconditioned secretion and increased sensitivity to cholinomimetics, i.e., reflex-humoral dissociation, are characteristic of the first, milder stage of denervation, arising 10-14 days after acute trauma. Later, however, after 1-2 months or sometimes after a few years, a more profound degree of denervation develops progressively and responses to cholinolytics (atropine, scopolamine, oxyphenonium) 20-30 min after subcutaneous injection are reversed, i.e., a clear form of atropine paradox is observed. In some patients (35 subjects) the denervation syndrome did not progress, i.e., stage I of denervation was stabilized. In 55 subjects the paradox was seen in a clear form.

In 20 subjects the paradox was masked or latent in type, and to bring it to light additional stimulation (induction) by a very weak food or acid stimulus was necessary in addition to atropinization.

Let us examine this latent form of atropine paradox, not previously described. The group of subjects consisted of 12 patients with injury to the base of the skull, five patients after radical operation on the ear for chronic suppurative otitis with caries of the walls of Fallopius' canal, two patients after removal of an acoustic neurinoma (previously suffering from chronic otitis), and one patient with a glomus tumor of the petrous temporal bone. In the last three patients the level of paradoxical secretion was depressed because the patients had not been treated by x-ray therapy (in the parotid region).

EXPERIMENTAL METHOD

The technique includes elements of restorative therapy because atropine is widely used for the treatment of craniocerebral trauma [8]. Durgs acting on the autonomic nervous system were used (in small doses) to characterize autonomic functions and to determine the level of the lesion, the time course and progressiveness of the disease, and its stability or restitution. Lashley-Krasnogorskii capsules were fixed on the efferent ducts of the parotid glands on the denervated and normal (control) sides. Secretion was recorded as follows: spontaneous, in response to swallowing 30 ml of 0.5% citric acid, after subcutaneous injection of cholinomimetics (0.5 ml of 1% pilocarpine, 0.5 ml of 1:5000 carbachol), after injection of

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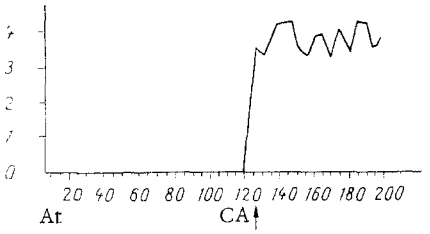

Fig. 1. Conversion of cholinolytic action of atropine into cholinomimetic. Here and in Figs. 2 and 3: abscissa, time (in min); ordinate, secretion (in ml). At) 0.1% atropine, 1.0 ml, subcutaneously; CA) 0.5% citric acid solution given after 120 min.

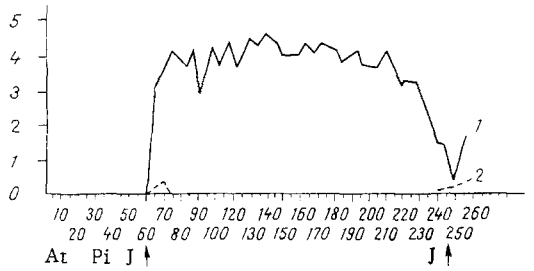

Fig. 2. Transformation of cholinomimetic action of atropine into cholinomimetic. Inhibition by atropine (0.1% At, 0.6 ml), of pilocarpine (1% Pi, 0.75 ml) injected at 26th minute. Paradox revealed at 60th minute after induction (15 drops of orange juice — J). Reactivation of paradox at 240th minute (five drops of orange juice —J); 1) denervated, 2) intact gland. Patient Z., woman aged 49 years. Fraction of petrous temporal bone.

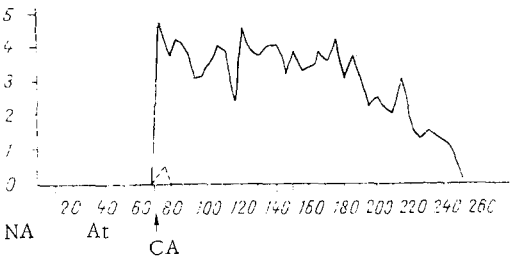

Fig. 3. Inhibition of atropine secretion by noradrenaline and its appearance after induction. Manifest form of paradox. NA) 0.1% noradrenaline 0.5 ml, subcutaneously; At) 0.1% atropine, 0.5 ml, subcutaneously; CA) citric acid solution. Patient S., woman aged 46 years. Otogenic operation.

cholinolytics (0.3-1.0 ml of 0.1% atropine subcutaneously, intramuscularly, intravenously, and perorally; 1:2000 scopolamine, 0.1% oxyphenonium, 0.1% tropazine), after injection of 1.0 ml of 0.05% neostigmine, and after injection of catecholamines (adrenaline, noradrenaline, isoprenaline) in small doses. The tests were repeated many times in the course of several years on each subject.

EXPERIMENTAL RESULTS

All four features of stage I of denervation were present in all 20 subjects. Atropine caused the usual cholinolytic effect, i.e., it did not excite secretion and blocked pilocarpine secretion of saliva, just as in the control, intact gland. If however, atropine blockade

TABLE 1. Latent Form of Atropine Paradox — Change from Cholinolytic Effect of Atropine and Mixture of Atropine and Pilocarpine to Cholinomimetic after Stimulation with 0.5% Citric Acid (3.0-15.0 ml)

Serial No.	Surname, initial	Age, years	Diagnosis	Date	Substance injected	Mode of administration	Duration of negative phase before stimulation (induction), min	Positive phase after stimulation (induction)		
								duration of observation, min	secretion, ml	
									denervated gland*	intact gland†
1	K.	38	Head injury	5/9	0,1% atropine (0,5 ml) + 1% pilocarpine (0,5 ml)	Subcutaneously	150	200	158,0	3,2
				5/14	0,1% atropine (0,5 ml) + 1% pilocarpine (0,5 ml)	"	47	228	190,0	2,0
				5/23	0,1% atropine (0,4 ml)	"	47	88	42,7	1,8
				10/18	0,1% atropine (0,75 ml)	"	25	105	56,9	0,6
2	p.	33	Otogenic operation	6/16	0,1% atropine (1,0 ml) + + 1% pilocarpine (0,5 ml)	"	50	130	39,0	0,0
3	K-n	37	Same	6/16	0,1% atropine (0,5 ml) + + 1% pilocarpine (0,5 ml)	"	71	120	54,6	2,0
4	S-v	25	"	5/22	0,1% atropine (0,5 ml) + + 1% pilocarpine (0,5 ml)	"	50	115	44,7	6,8
5	E.	38	"	12/20	0,1% atropine (0,3 ml)	Intravenously	30	120	35,0	0,25
				2/4	0,1% atropine (0,5 ml) + 1% pilocarpine (0,5 ml)		60	150	34,2	1,8
6	Z.	57	Head injury	3/26	0,1 % atropine (0,5ml)	"	10	160	75,4	2,7
				2/5	0,1% atropine (0,5 ml) + + 1% pilocarpine (0,5 ml)	"	50	130	79,4	0,3
7	P-v	41	Same	9/18	0,1% atropine (1,0 ml)		148	105	74,0	0,0
8	F.	41	"	2/21	0,1% atropine (0,6ml)	Subcutaneously	45	175	64,0	0,0
9	N.	19	"	2/27	0,1% atropine (0,6ml)	"	40	120	51,2	0,0
10	S-na	47	Neurinoma	1/19	0,1% atropine (0,5ml)	"	45	105	40,9	0,0
				1/28	0,1% atropine (0,9 ml)	"	35	85	34,0	0,0
11	G.	26	Same	2/13	0,1% atropine (0,5 ml) + + 1% pilocarpine (0,5 ml)	"	40	95	43,0	0,3
12	S-va	42	Glomus tumor of petrous temporal	3/31	0,1% atropine (0,5 ml) + + 1% pilocarpine (0,5 ml)	"	50	80	25,7	1,4
				4/20	0,1% atropine (0,6 ml)	"	25	95	21,2	0,1

*Figures given for duration of positive phase and level of secretion are below those actually observed for, because of a long period of observation, it had to be terminated while intensive secretion was still going on, so as not to fatigue the subject.
†Effect chiefly to unconditioned stimulus.

was accompanied by reflex stimulation of the oral cavity, even if very weak (for example, a tiny fragment of liver or a few drops of fruit juice or dilute citric acid), a rapid salivatory response to atropine appeared very quickly, just as in a weak solution (0.5%) of citric acid was given 120 min after injection of 1.0 ml atropine, a rapid salivatory response of the denervated gland of explosive type quickly developed (Fig. 1).

After simultaneous injection of atropine and pilocarpine secretion was very weak or absent altogether from both the denervated and the intact gland. Complete blockade of secretion could last 4-6 h, i.e., until complete elimination of the atropine. Against the background of blockade, however, reflex stimulation (induction) instantaneously transformed the cholinolytic effect of atropine into cholinomimetic (Fig. 2).

The latent form of the atropine paradox was converted into the manifest form only by reflex acid or food stimulation. Temperature, photic, or tactile stimulation and also injection of anticholinesterase, cholinomimetic, and adrenergic drugs were all ineffective.

In turn, the manifest form of the paradox could be transformed into latent if catecholamines (adrenaline, noradrenaline, isoproteranol, ergotamine) were injected 15-30 min before atropine. In these cases additional food or acid stimulation abolished the blockade, and with the onset of atropine secretion, the artificially evoked latent form became manifest (Fig. 3).

Depending on activation of the repressive (catecholamines) or depressive factor (induction), atropine thus plays the role of antagonist or agonist (with the possibility of switching its action) depending on the special state of mobility of function of the gland deprived of its nervous control. Addition or withdrawal of the "repressor" determines the outcome of the reaction in these cases, that is, either negative or positive (Table 1).

The atropine paradox, in both its manifest and latent forms, is in harmony with the concept of an increase in specificity of acetylcholine receptors in the course of evolution and, conversely, loss of selectivity and adequacy after denervation [3-5]. An excitatory action of cholinolytics has been described on denervated and protein-sensitized dog's muscle, and also in tissue culture on rabbit muscle symplasts, where even tubocurarine had an excitatory action. The mechanism of the latent form of the paradox is difficult to explain at present. It can be tentatively suggested that reflex stimulation evokes liberation of a certain substance into the blood stream, which is transported by the humoral route to the denervated gland and induces the appearance of atropine secretion. It is unlikely that this substance is acetylcholine, which enters the blood stream in extremely small amounts and is instantly destroyed in it. It is possibly some other, as yet unknown, factor.

Under normal conditions there are two types of salivatory reactions: reflex and humoral, due to the presence of double synaptic and extrasynaptic regulation. After denervation three other types of reactions appear in succession: 1) with increased sensitivity to cholinomimetics (stage I); 2) with the latent form of conversion of the reaction to cholinolytics; 3) with the manifest form of reversed reaction to cholinolytics.

In clinical observations during 1980-1981 (Clinic for Nervous Diseases and Neurosurgery, Heads Professor A. M. Dorovin and Professor B. M. Nikiforov) the order of appearance of all three stages of the postdenervation syndrome of the tympanic nerve was established precisely. During restitution, this sequence was observed in the opposite order. Taken as a whole, i.e., during reflex and humoral reactions under normal conditions and potential reactions after denervation, five basic types of responses of the human parotid salivary gland, manifested through the intervention of the corresponding cholinergic structures with affinity for cholinergic ligands, were distinguished.

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