CHANGES IN THE ACETYLCHOLINE AND NORADRENALIN LEVELS IN THE RAT BRAIN PRODUCED BY CHOLINOMIMETICS AND ADRENOMIMETICS

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UDC 612.822.2.014.46:615.217.22

Excitation of adrenergic systems (by amphetamine) in the brain leads to utilization of the acetylcholine reserves whereas excitation of cholinergic systems (by arecoline) causes utilization of the noradrenalin reserves. Meanwhile amphetamine does not liberate acetylcholine from isolated nerve endings and arecoline has no effect in vitro on the processes of noradrenalin storage.

Functional relations between cholinergic and adrenergic mediator systems in the brain during selective excitation of one of them with the aid of mimetics has not yet been unanimously explained. The reason for this difference of opinion is the inadequate study of the biochemical mechanism of action of cholinomimetics and adrenomimetics on the brain. For example, the sympathomimetic action of amphetamine on the CNS is due to the liberation of noradrenalin (NA) from the presynaptic depots [5, 6]. At the same time, the writers have shown [2] that by the action of amphetamine on the rat brain, liberation of NA is followed by a clear decrease in the acetylcholine (AC) concentration. These observations show that during sudden excitation of the adrenergic systems of the brain marked activation of cholinergic processes takes place. The question thus arises of the state of the adrenergic processes of the brain during sudden excitation of cholinergic systems by means of cholinomimetics as well as the mechanism of these effects of adrenomimetics and cholinomimetics.

In the investigation described below the effects of amphetamine and arecoline on the AC and NA concentrations in the rat brain were compared, and the effect of these drugs on the storage of AC and NA in isolated nerve endings (synaptosomes) was studied.

EXPERIMENTAL METHOD

Male albino rats weighing about 200 g were used. Aqueous solutions of arecoline (10 mg/ml) and amphetamine (5 mg/ml) were injected intraperitoneally in a dose of 0.1 ml/100 g body weight. The control animals received water. The criterion of the arecoline effect was a brief (lasting a few seconds) attack of tremor in the animals immediately after injection of the drug. The criterion of the amphetamine effect was motor excitation of the animals, starting 5-10 min after the injection. The brain (without the cerebellum) was removed, freed as far as possible from blood, weighed, and the NA and AC were extracted and estimated quantitatively as described previously [1, 2].

The methods used to isolate the synaptosomes and to study the effects of the pharmacologically active substances on the storage of NA and AC in them were described previously [1].

EXPERIMENTAL RESULTS AND DISCUSSION

After administration of arecoline to the animals the AC concentration in the brain increased slightly (Table 1), while after administration of amphetamine, on the other hand, it fell significantly.

(Presented by Academician of the Academy of Medical Sciences of the USSR S. N. Golikov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 76, No. 11, pp. 74-76, November, 1973. Original article submitted February 26, 1973.

TABLE 1. Concentration (in μg/g) of AC and NA in the Rat Brain Following Administration of Arecoline and Amphetamine

Parameter	AC				NA			
	control	arecoline	control	amphetamine	control	arecoline	control	amphetamine
M ± m	2,6 ± 0,4	3,1 ± 0,5	2,1 ± 0,15	1,5 ± 0,15	0,42 ± 0,02	0,31 ± 0,01	0,47 ± 0,01	0,29 ± 0,02
Per cent of control	—	119	—	75	—	74	—	62
n	5	5	4	4	4	4	3	3
P	>0,05		<0,05		<0,005		<0,001	

TABLE 2. Content (in μg per sample) of AC and NA in Isolated Nerve Endings after Incubation with Amphetamine (5 μg/ml) and Arecoline (10 μg/ml)

Parameter	AC		NA		
	control	amphetamine	control	amphetamine	arecoline
M ± m	0,59±0,03	0,63±0,04	0,85±0,06	0,54±0,03	0,88±0,04
Per cent of control	—	107	—	63	104
n	3	3	3	3	4
P	>0,05		<0,005		>0,05

The NA concentration was substantially reduced by the action of both the adrenomimetic and the cholinomimetic; the exhaustion of the NA reserves was greater in the case of amphetamine.

To determine whether the action of these drugs on the liberation of NA and AC from their presynaptic depots is direct or indirect, investigations were carried out on isolated synaptosomes. This method has been used previously to prove the direct participation of muscarinic and nicotinic cholinolytics in the storage of AC and NA in presynaptic structures [1, 3].

These experiments showed that amphetamine (5 μg/ml) does not induce liberation of AC from isolated synaptosomes (Table 2), whereas it substantially exhausts the NA reserves (by about 40%). In these experiments the amphetamine concentration was chosen to be 5 μg/ml because amphetamine is distributed uniformly in the body and, consequently, this concentration corresponds to a dose of 5 mg/kg.

The effect of arecoline on the storage of NA was studied under similar conditions. The arecoline concentration in the medium was 10 μg/ml and was chosen for the same reason as that of amphetamine. No significant effect of arecoline was found on the liberation of NA from the synaptosomes (Table 2). In addition, some tendency toward the "occlusion" of NA in the synaptosomes was seen.

Excitation of adrenergic systems in the CNS by the action of amphetamine (consisting essentially of the liberation of NA from presynaptic reservoirs) thus led to the utilization of the AC reserves. Excitation of the cholinergic systems by arecoline (as a result of its direct reaction with cholinergic receptors) caused utilization of the NA reserves. The results of the experiments with synaptosomes show that amphetamine has no direct effect on the storage of AC, and in exactly the same way arecoline does not liberate NA from synaptosomes. Meanwhile, amphetamine under identical conditions liberates NA from synaptosomes in vitro just as it does in vivo. Consequently, the decrease in the AC concentration in the brain after administration of amphetamine and the decrease in NA after administration of arecoline are the results of secondary liberation of the mediators.

It is not yet possible to explain the mechanism of this phenomenon beyond all possible doubt. Bearing in mind the probability of alternation of cholinergic and adrenergic neurons in the neuronal chains of the brain [7], the consecutive involvement of the two types of neurons in excitation, with the corresponding utilization of the mediator reserves, can be assumed. On the other hand, considering the polyreactivity of the brain neurons, caused by the existence of synapses with different chemical properties [4], it can be postulated that the secondary involvement of the adrenergic component during excitation of cholinergic receptors (or vice versa) takes place by the feedback principle and evidently acts as a regulator in excitation processes.

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