EFFECT OF PSYCHOTROPIC DRUGS ON SOME ASPECTS OF ACETYCHOLINE METABOLISM IN THE CAT BRAIN

A. R. Bandman, L. V. Smirnova, and G. A. Sofronov

UDC 615.214.2.015.45:612.822.2

The synthesis of acetylcholine, its liberation, and its level in the cerebral cortex and the content of mediators in the mesencephalon were studied in intact cats and in cats receiving benactyzine, chlorpromazine, and trifluoroperazine. Benactyzine increased the liberation of acetylcholine by the cortex and reduced the content of the bound fraction of the mediator in the cerebral cortex and mesencephalon. Chlorpromazine increased the liberation and the content of free acetylcholine in the tissues of the cortex and mesencephalon. Under the influence of trifluoroperazine the intensity of liberation of mediator by the cortex was reduced, while the level of its free fraction in the cortex rose. The choline-acetyltransferase activity was unchanged under these experimental conditions.

Many psychotropic drugs belonging to different classes of chemical compounds and producing different pharmacological effects interfere directly or indirectly with the metabolism of acetylcholine (AC) in the CNS. Details are given in the literature of the effect of some central cholinolytics on the content and liberation of AC in the brain [1-6]. Information is given on the ability of neuroleptics to modify the synthesis and liberation of AC in the brain tissues of experimental animals [8, 9, 11]. However, the available information is not sufficient to allow the role of changes in AC metabolism in the pharmacological action of psychotropic drugs to be assessed.

This paper gives details of the effect of the tranquilizer benactyzine and the neuroleptics chlorpromazine and trifluoroperazine on processes connected with the synthesis, storage, and liberation of AC in the brain of animals.

EXPERIMENTAL METHOD

Experiments were carried out on cats weighing 3-4 kg. The animals were divided into two groups. Group 1 consisted of cats decapitated 1 h after receiving test drugs or physiological saline. The content of free and bound AC in their cerebral cortex and mesencephalon was studied by the method of Crossland and Slater [5]. The AC content was expressed in μg/g wet tissue. Activity of choline-acetyltransferase (2.3.1.6) in the cerebral cortex was studied by Hebb's method [7]. Activity of this enzyme was estimated from the amount of AC synthesized by 1 g dried tissue of the cerebral hemispheres and calculated as a percentage of the control. Liberation of AC by the cortex was studied in the animals of group 2 by a modified [3] method of MacIntosh and Oborin [10]. In the modified method it was possible to estimate the intensity of AC liberation in animals behaving freely. A hollow cylindrical chamber of transparent plastic, with an internal diameter of 7 mm and a height of 8 mm, was implanted into the skull of the cats. The chamber was placed directly on the pia mater in the parietal region. A plastic rod was screwed into the hollow interior of the chamber to a distance of 1-1.5 mm from the brain surface. Nichrome cortical electrodes were inserted contralaterally to record the EEG. On the third day after the operation the rod was removed and the chamber filled with physiological saline containing eserine (1×10^{-4} g/ml) warmed to 38°C. After 30 min the eserine concentration was reduced to 5×10^{-6} g/ml, and throughout the experiment the solution in the chamber was changed every quarter of an hour. The AC content was determined in the samples and expressed in ng/cm^2 cortical surface in 15 min.

S. M. Kirov Military Medical Academy, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 76, No. 7, pp. 56-58, July, 1973. Original article submitted May 10, 1972.

TABLE 1. Liberation of AC by Cerebral Cortex after Injection of Benactyzine, Chlorpromazine, and Trifluoroperazine into Cats

Drug and dose (in mg/kg)	No. of experiments	Content of acetylcholine (in ng/cm² in 15 min			
		before injection of drugs (background)	after injection of drugs		
			30 min	60 min	90 min
Benactyzine (0.2)	4	5,5±0,3	8,3±0,3	11,4±1,1	7,0±0,3
P			<0,01	<0,01	<0,05
Chlorpromazine (1) . . .	3	6,0±0,7	6,2±0,4	8,8±0,4	7,2±0,5
P				<0,05	>0,05
Trifluoroperazine (0.05).	3	6,1±0,6	3,3±0,6	3,3±0,6	
			<0,05	<0,05	

TABLE 2. AC Content in Cerebral Cortex and Mesencephalon of Cats under Influence of Benactyzine, Chlorpromazine, and Trifluoroperazine

Drug and dose (in mg/kg)	AC content (in μg/g wet tissue)					
	cerebral cortex			mesencephalon		
	n	free	bound	*n*	free	bound
Intact animals	30	0,44±0,03	0,38±0,02	6	1,63±0,02	1,49±0,13
Benactyzine (0.2)	6	0,44±0,03	0,24±0,02	6	1,80±0,13	1,13±0,07
P			<0,01			<0,05
Chlorpromazine (1) . .	9	0,64±0,06	0,46±0,04	9	2,10±0,13	1,48±0,10
P		<0,001			<0,05	
Trifluoroperazine (0.05)	6	0,59±0,03	0,52±0,11	6	1,54±0,07	1,26±0,10
P		<0,05				

The EEG was recorded with a Nihon-Kohden electroencephalograph. In all the methods used AC was determined by a biological method on the eserinized dorsal muscle of the leech.

Drugs were injected intramuscularly in the following doses: benactyzine 0.2 mg/kg, chlorpromazine 1 mg/kg, and trifluoroperazine 0.05 mg/kg.

EXPERIMENTAL RESULTS

Under the influence of benactyzine the choline-acetyl transferase activity was virtually unchanged and amounted to 90% of the control level. Liberation of AC by the cortex rose sharply, while the bound fraction of the mediator in the cortex and mesencephalon decreased at the same time (Tables 1 and 2). Slow high-amplitude waves were recorded in the EEG. Chlorpromazine likewise did not change the choline-acetyl-transferase activity (91% of the control). A very slight increase in liberation of AC by the cortex was observed 1 h after injection of the neuroleptic. The content of free AC in the cortex and mesencephalon rose. Synchronized activity predominated in the EEG during the period of increased AC liberation. No change in choline-acetyltransferase activity was found after administration of trifluoroperazine to the cats (94% of the control). Trifluoroperazine reduced the intensity of AC liberation by the cortex, but at the same time the concentration of the free form of mediator in the cortex rose. The content of both fractions of AC in the mesencephalon was unchanged compared with the control. In the dose used, trifluoroperazine did not affect the EEG.

It follows from the results of these experiments that, unlike trifluoroperazine, benactyzine and chlorpromazine increased the liberation of the mediator. This effect can evidently be connected with the central muscarine-like cholinolytic properties of benactyzine and chlorpromazine, for it was observed when they were used in doses leading to the appearance of slow activity in the EEG, whereas trifluoroperazine did not change the electrical activity of the brain.

Elevation of the free AC level by chlorpromazine and trifluoroperazine was evidently attributable neither to a change in the synthesis of the mediator (since the choline-acetyltransferase activity was unchanged under these experimental conditions, nor to a change in its liberation (which was increased by the

action of chlorpromazine but reduced by trifluoroperazine). The similar effects of chlorpromazine and trifluoroperazine on the accumulation of free AC suggest a possible connection with the neuroleptic action of both these drugs, although this problem requires further study.

The considerable and prolonged increase in the liberation of AC under the influence of benactyzine, while its synthesis is unchanged, is evidently responsible for the lowered level of the bound form of the mediator in the brain tissues.

LITERATURE CITED

1. L. A. Gromov and V. B. Litvinov, in: Current Problems in Pharmacology [in Russian], Kiev (1971), p. 79.
2. L. A. Gromov and K. N. Lokhvitskaya, in: Pharmacology and Toxicology [in Russian], No. 6, Kiev (1971), p. 24.
3. G. A. Sofronov, in: Current Problems in Pharmacology [in Russian], Kiev (1971), p. 260.
4. L. Beani, C. Bianchi, P. Megazzini, et al., Biochem. Pharmacol., 18, 1315 (1969).
5. J. Crossland and P. Slater, Brit. J. Pharmacol., 33, 42 (1968).
6. J. D. Dudar and J. C. Szerb, J. Physiol. (London), 203, 741 (1969).
7. C. Hebb, in: Handbuch der Experimentallen Pharmacologie, Berlin (1963), p. 55.
8. K. Jamandas, J. W. Phillis, and C. Pinsky, Brit. J. Pharmacol., 43, 53 (1971).
9. A. I. Mandell and S. Knapp, Neuropharmacology, 10, 513 (1971).
10. F. C. MacIntosh and P. E. Oborin, in: 19th International Physiological Congress, Montreal (1953), p. 580.
11. G. Pepeu, and A. Bartolini, Europ. J. Pharmacol., 4, 254 (1968).