THE EFFECT OF CHLORPROMAZINE ON THE ACETYLCHOLINE CONTENT OF CERTAIN AREAS OF DOG BRAIN

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The level of acetylcholine in the brain has been shown to vary with its functional activity. Such variations have been related to physiological changes in nervous activity such as sleep or wakefulness (11) to the action of neuropharmacological agents (14,11, 4) and to certain physical stresses, such as electrical stimulation (11).

Malhotra and Pundlik (7) observed that after reserpine, there was increase in the acetylcholine content of the hypothalamus, the temporal lobe, the frontal lobe, the cerebellum, and the spinal cord whilst there was decrease in the hippocampus. Malhotra and Mehta (8), reported that after meprobamate, there was significant increase in the acetylcholine content of the hypothalamus and the hippocampus and correlated their findings with the electrical changes in these areas of the brain after meprobamate. Takahashi *et al.*, (13) have reported that after chlorpromazine (CPZ), there is no significant effect in the acetylcholine content in rat whole brain. It may, however, be mentioned that the metabolism of different areas of the brain differs considerably (9, 5). Thus, a mild degree of hypoxia may selectively induce metabolic changes in central nervous system which may not be apparent if judged by the metabolism of the brain as a whole. The same may be true as far as neurohormones are concerned and the estimation of neurohormones of the whole brain may not throw much light on their metabolism in health, disease or after drugs. It was, therefore, considered worthwhile to study the effect of CPZ, a phenothiazine tranquillizer on the acetylcholine content of certain selective areas of central nervous system of dog.

MATERIALS AND METHODS

The experiments were performed on thirty healthy mongrel dogs of either sex weighing between 4 and 13 *Kg*. The dogs were divided into 5 groups of six each. Group 1, served as control and in this group, equivalent volume of saline was given intravenously. Group 2 and 3 received 5 *mg/kg* of CPZ and group 4 and 5 received 10 *mg/kg* of CPZ. The control animals were interspersed between the experiments with CPZ. The animals were anaesthetised with ether after 45 and 90 minutes of each dose of chlorpromazine, bled to death through carotid arteries, skull opened and the following portions of the brain were removed quickly and transferred to weighing bottles which had already been kept in freezing mixture at 4°C; the hypo-

thalamus, the hippocampus, the anterior portion of the frontal cortex and the mid brain with the exception of colliculi, the basis pedunculi and brachium colliculi inferioris.

Acetylcholine was extracted from the portions of the brain in acidified frog-ringer solution containing physostigmine at 95° to 100°C, and was assayed on frog rectus abdominis muscle by the method of Nachmasohn, as modified by Anand (1).

RESULTS

The acetylcholine concentration of the different areas of dog brain after CPZ as compared to control dogs under ether anaesthesia is given in Table I. Dogs treated with CPZ 5 *mg/kg* showed significant increase of acetylcholine in the frontal cortex when estimated after 90 minutes but the change was insignificant when estimated after 45 minutes. CPZ 10 *mg/kg* produce d significant increase of acetylcholine in the frontal cortex after 45 and 90 minutes. The variations in the acetylcholine concentrations in other areas of dog brain after 5 and 10 *mg/kg* of CPZ after 45 and 90 minutes were insignificant.

TABLE I

The Acetylcholine concentration of different areas of the central nervous system in normal and chlorpromazine treated dogs under ether anaesthesia

Drug & dose/*kg* body weight	No. of animals	Acetylcholine concentration in ug/g (mean±S.D.)			
		Hypothalamus	Hippocampus	Frontal cortex	Midbrain
Control	6	2.940±1.07	3.275±0.59	1.046±0.17	2.772±0.43
CPZ 5mg (45 minutes)	6	2.389±0.80	3.072±0.55	2.038±0.65 P>0.1	2.300±0.40
CPZ 5mg (90 minutes)	6	2.597±0.95	2.558±1.15	2.842±1.08 P<0.01	2.101±0.88
CPZ 10mg (45 minutes)	6	2.874±0.96	3.650±0.86	1.606±0.29 P<0.01	2.604±0.89
CPZ 10 mg (90 minutes)	6	3.198±0.51	2.762±0.80	2.196±1.05 P<0.05	2.344±0.92

The results are mean and standard devations expressed as ug/g brain tissue. Probability of no difference between the control and the drug treated animals calculated by 't' test.

DISCUSSION

The present findings indicate that after CPZ, there is selective and significant effect on the acetylcholine content of the frontal cortex, while the effect is insignificant on the acetylcholine content of hypothalamus, the hippocampus and the mid brain.

Dobkin *et al.*, (3) observed that the primary effect of CPZ involves reduction in the stimuli which reach the medial reticular formation inducing a state of wakefulness by cephalic influences upon the cerebral hemispheres, while permitting normal sensory and cerebration responses. They showed that CPZ almost completely suppressed acetylcholine release from the cat cortex in doses of 30 *mg/kg*. It was also observed that in human beings suffering from long standing schizophrenia, there was slight depression of acetylcholine release after CPZ from the frontal cortex removed after prefrontal lobotomy. Tower *et al.*, (15) and Penfield *et al.*, (10) postulated that the behavioural disturbances may be related to disturbances in acetylcholine synthesis and release from cerebral cortex. Longo *et al.*, (6) suggested that CPZ exerts depressant effects on the medial ascending reticular activating system through 'cholinergic' blockade. They observed that in rabbits the depressant effects of CPZ on "arousal" responses could be reversed by physostigmine but not by amphetamine, serotonin, epinephrine and acetylcholine CPZ is known to exert its peripheral antiacetylcholine action (12). It is quite possible that it might have a similar central action. Bernsohn *et al.*, (2) found that CPZ inhibits cytochrome oxidase and ATP ase.

The increase in the acetylcholine content of the frontal cortex in the present study may be due to any one or the combination of the following factors :—(*a*) increased synthesis due to inhibition of ATP ase, (*b*) decreased release from the cortex, (*c*) central cholinergic blockade.

Significant increase in acetylcholine content in frontal cortex after 90 minutes of 5 *mg/kg* of CPZ and after 45 and 90 minutes of 10 mg/kg of CPZ may be due to the fact that with low doses (5 *mg/kg*) maximum effect is attained after a longer duration while with larger doses (10 *mg/kg*) maximum effect is attained sooner.

SUMMARY

1. The effect of intravenous CPZ on the acetylcholine concentration of the hypothalamus, the hippocampus, the frontal cortex and the mid brain has been studied on dogs under ether anaesthesia.

2. There was significant increase in acetylcholine content of the frontal cortex when estimated after 90 minutes of 5 *mg/kg* of CPZ but the change was insignificant when estimated after 45 minutes. CPZ 10 *mg/kg* produced significant increase of acetylcholine in the frontal cortex after 45 and 90 minutes. In other areas of brain studied, the changes were insignificant.

3. Attempts have been made to explain the mechanism of increase in the acetylcholine content of the frontal cortex.

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