EFFECT OF CHOLINOLYTIC HALLUCINOGENS ON ACETYLCHOLINE CONTENT OF CERTAIN PARTS OF RABBIT BRAIN

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The central stimulatory actions of atropine causing excitement, tremors and hallucinations in high doses are well known. Giarmann and Pepeu (1) showed that atropine and hyoscine reduced the total acetylcholine content of brain. Further it has been suggested that among certain cholinolytic hallucinogens (like atropine and hyoscine), the psychotomimetic activity may be linked with an alteration in the total acetylcholine level of brain (2, 3). It is also known that rabbits are resistant to the central psychotomimetic actions of atropine which are commonly seen in man and other experimental animals with high doses of these drugs. It was therefore considered worthwhile to examine the effect of atropine and hyoscine on the acetylcholine content of different parts of rabbit brain.

MATERIAL AND METHODS

Albino rabbits, 1-2.2 kg were selected for study. The drugs (atropine sulphate and hyoscine hydrobromide) were dissolved in from 0.1 to 0.5 ml of 0.9% saline and injected slowly in the marginal ear veins of rabbits. Control animals, examined with each experiment, were given equivalent volumes of 0.9% saline by the same route. The doses of all drugs have been expressed as salts.

The animals were bled to death 30 minutes after the injection of drugs. The skull was opened and the following areas of the brain were quickly removed the hypothalamus, cerebral cortex, mid brain, cerebellar cortex and medulla.

The parts were transferred quickly to weighing bottles which had already been kept in freezing mixtures and the acetylcholine extracted by trichloroacetic acid, after the method of Smallman and Fisher (4). The acetylcholine content of the extracts was estimated within 24 hours by bioassay on the frog isolated rectus abdominis muscle preparation; the muscle was bathed in frog Ringer solution containing physostigmine (1 mg/100 ml).

RESULTS

The acetylcholine concentrations of the different parts of rabbit brain with atropine and hyoscine as compared to control animals are given in Table 1. Rabbits treated with

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TABLE 1. The acetylcholine concentrations of different parts of brain in normal and atropine and hyoscine treated rabbits.

Drugs	Dose mg/kg	No. of animals	Acetylcholine concentration in $\mu\text{g/g}$ (mean $\pm$ S.D.)				
			Cerebral cortex	Hypothalamus	Mid brain	Cerebellar cortex	Medulla
Control	-	9	2.36	2.85	1.53	0.66	1.31
Atropine sulphate	10	6	1.75	2.43	1.49	0.58	1.28
			± 0.58 < .01	± 0.67 < .01	± 0.29 < .05	± 0.11 < .05	± 0.11 < .01
Atropine sulphate	20	6	1.48	2.28	1.44	0.60	1.25
			± 0.41 < .05	± 0.71 < .01	± 0.32 < .01	± 0.09 < .05	± 0.38 < .05
Hyoscine hydrobromide	2.5	7	1.58	2.31	1.48	0.55	1.19
			± 0.62 < .01	± 0.46 < .01	± 0.21 < .05	± 0.14 < .01	± 0.47 < .05
Hyoscine hydrobromide	5	6	1.12	1.87	1.41	0.59	1.17
			± 0.31 < .01	± 0.43 < .05	± 0.13 < .01	± 0.17 < .05	± 0.23 < .05

The results are means and standard deviations expressed as $\mu\text{g/g}$ of brain tissue. The significance of the differences between means of results of control and drug treated are calculated by "t" test.

atropine (10 and 20 mg/kg) show a significant decrease of acetylcholine in the hypothalamus and cerebral cortex. Hyoscine (2.5 and 5 mg/kg) was found to be more potent in reducing the acetylcholine content in the same regions of brain.

DISCUSSION

The level of total acetylcholine in the brain has been shown to vary with the functional activity of the brain (5). These alterations have been associated with drug and electrically induced convulsions (6), physiological changes in nervous activity such as sleep or wakefulness (7), the action of certain neuropharmacological agents (8), and certain physical agents, such as changes in temperature (9), and electrical stimulation (7). Giarman and Pepeu (1), however, showed that atropine and hyoscine produced significant reductions in the total acetylcholine content of the whole brain of rats without any gross changes in behaviour or evidence of excitation.

The central actions of atropine are not well understood inspite of a large amount of work done on it. Gaddum (10) considers it a medullary stimulant which ultimately leads to depression; while according to Loeb, Magni and Rossi (11), it has got a suprachiasmatic site of action. Atropine also potentiates the barbiturate induced anaesthesia (12), though causing the behavioral alerting (13). As referred earlier it has also been observed that among certain cholinolytic psychotomimetic drugs (like atropine and hyoscine), the psy-

chotomimetic effects may be linked with alterations in brain acetylcholine level (2, 3).

It is well known that rabbits are resistant to the central and psychotomimetic actions of atropine and hyoscine; yet according to our results, they lower the acetylcholine content in certain parts of the brains of these animals. It has been suggested that the EEG activating system is fundamentally cholinergic in rabbits (14). The electroencephalographic studies also indicate that these drugs induced a synchronous (high voltage, low frequency waves) EEG pattern in rabbits and also blocked the EEG activation induced by physostigmine (14). Similarly both the drugs have been reported to depress spontaneous EEG activity in man (15) and in unanaesthetized dogs, atropine caused "burst slow wave" EEG patterns similar to the barbiturate induced "sleep pattern" (13). The reduction in the acetylcholine content of rabbit cerebrum and hypothalamus, after atropine and hyoscine, seems to correlate not only with the psychotomimetic action of these drugs but also with their potency in inducing amnesia in the rat (16) and electrophysiological changes in rabbit and other experimental animals (11, 13).

SUMMARY

1. The effect of intravenous atropine and hyoscine on the acetylcholine concentration of the cerebral cortex, hypothalamus, mid brain, cerebellar cortex and medulla have been studied in rabbits.

2. There was a significant decrease in the acetylcholine content of the hypothalamus and cerebral cortex after atropine and hyoscine, while in other parts of brain studied the changes were not marked. Hyoscine was found to be more potent than atropine in this respect.

3. The significance of these selective changes in the acetylcholine content of certain parts of brain has been discussed. An attempt has been made to correlate these changes with electrical changes in the brain after atropine and hyoscine.

REFERENCES

- 1) GIARMAN, N.J. AND PEPEU, G.: *Br. J. Pharmac. Chemother.* **19**, 226 (1962)
- 2) GIARMAN, N.J. AND PEPEU, G.: *Ibid.* **23**, 123 (1964)
- 3) GIARMAN, N.J. AND FREEDMAN, D.X.: *Pharmac. Rev.* **17**, 1 (1965)
- 4) SMALLMAN, B.N. AND FISHER, R.W.: *Can. J. Biochem. Physiol.* **36**, 575 (1958)
- 5) CROSSLAND, J. AND MERRICK, A.J.: *J. Physiol.* **125**, 56 (1954)
- 6) FELDBERG, W.: *Acetylcholine, Metabolism of the Nervous System*, Edited by RICHTER, D., p. 494, Pergamon Press, London (1957)
- 7) RICHTER, D. AND CROSSLAND, J.: *Am. J. Physiol.* **159**, 247 (1949)
- 8) ELLIOTT, K.A.C., SWANK, R.L. AND HENDERSON, N.: *Ibid.* **162**, 469 (1950)
- 9) ANAND, B.K.: *Ibid.* **168**, 218 (1952)
- 10) GADDUM, J.H.: *Pharmacology*, 4th Ed., p. 103, Oxford University Press, London (1953)
- 11) LOEB, C., MAGNI, F. AND ROSSI, C.F.: *Archs ital. Biol.* **98**, 293 (1960)
- 12) MENSCH, H.M. AND DEJONGH, D.K.: *Acta physiol. pharmac. néerl.* **7**, 361 (1959)

- 13) WIKLER, A.: *Proc. Soc. exp. Biol. Med.* **79**, 261 (1952)
- 14) WHITE, R.P. AND BOYAJY, L.D.: *Archs int. Pharmacodyn. Thér.* **127**, 260 (1960)
- 15) OSTFELD, A.M. AND ARGUETE, A.: *J. Pharmac. exp. Ther.* **137**, 133 (1962)
- 16) DOMER, F.R. AND SCHUELLAR, F.W.: *Archs int. Pharmacodyn. Thér.* **127**, 449 (1960)