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EFFECT OF CHLORPROMAZINE AND RESERPINE ON THE CATECHOL AMINE CONTENT OF DIFFERENT AREAS OF THE CENTRAL NERVOUS SYSTEM OF THE DOG

BY

C. L. MALHOTRA AND K. PRASAD

From the Department of Pharmacology and Therapeutics, Lady Hardinge Medical College, New Delhi, India

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The effects of chlorpromazine and reserpine on the noradrenaline and adrenaline contents of the frontal cortex, the hypothalamus, the hippocampus and the midbrain were studied in the dog. In control dogs, the catechol amine concentrations were highest in the hypothalamus and lowest in the frontal cortex and the hippocampus. Noradrenaline contents were about seven to nine times as high as those of adrenaline in all the areas. Small doses of chlorpromazine raised the catechol amines in all the areas, the rise being maximum with 5 mg/kg. With increase in the dose of chlorpromazine there was a gradual reversal of the effect and, with 25 mg/kg, there was diminution of noradrenaline content in all the areas except in the hypothalamus. In general, chlorpromazine produced a greater rise in adrenaline than it did of noradrenaline content, and the increase of both amines was very high in the midbrain and the hippocampus compared with the other areas. Reserpine, however, depleted the catechol amine contents of all areas. The depletion was greatest for noradrenaline, an effect quite marked in the midbrain and the frontal cortex. It was concluded that the actions of these two tranquillizers on the catechol amines of dog brain differed both as to site and mechanism.

It is well established that reserpine depletes the brain stores of their noradrenaline content (Holzbauer & Vogt, 1956 ; Brodie, Olin, Kuntzman & Shore, 1957). However, chlorpromazine (25 mg/kg) causes little change in the noradrenaline content of the hypothalamus in the cat (Holzbauer & Vogt, 1954). Gey & Pletscher (1961) found no effect from 20 mg/kg of chlorpromazine on the noradrenaline content of whole rat brain. The present study was undertaken to obtain information about the effect of chlorpromazine on the catechol amine content of four areas of the central nervous system of the dog and to compare these effects with those of reserpine.

METHODS

Dogs of either sex were used. Groups of 5 dogs received 2, 5 or 25 mg/kg of chlorpromazine intravenously. One group of 10 dogs received 10 mg/kg chlorpromazine and another group of 10 dogs received 2 mg/kg reserpine. Fifteen untreated dogs served as controls. Two hr after administration of chlorpromazine and 4 hr after reserpine, the animals were anaesthetized with chloroform and bled through the carotid arteries. The skull was opened and the whole brain removed as quickly as possible. The following portions were removed with scissors and placed in labelled weighing bottles which had been kept in a freezing mixture at −4° C: (*a*) The anterior portion of the frontal cortex, (*b*) the hippocampus, (*c*) the entire hypothalamus,

and (*d*) the midbrain with the exception of colliculi, the basis pedunculi and brachium colliculi inferioris. The catechol amines were extracted from the brain samples and purified by the method described by Vogt (1953). Adrenaline and noradrenaline were separated chromatographically and assayed biologically on the rat blood pressure according to the procedure of Crawford & Outschoorn (1951). Before the start of bioassay, atropine sulphate 2 mg/kg, N-dimethylaminoethyl-N-p-chlorobenzyl-1-amino pyridine hydrochloride (Synopen) 5 mg/kg and hexamethonium tartrate 16 mg/kg were administered intravenously in the rat in this order at intervals of 10 min. The control experiments were always interspersed between those made with chlorpromazine and reserpine.

RESULTS

Noradrenaline and adrenaline contents of the hypothalamus, the hippocampus, the midbrain and the frontal cortex of the control dogs and the dogs after administration of chlorpromazine or reserpine are given in Tables 1 and 2 and Figs. 1 and 2.

TABLE 1

NORADRENALINE CONTENT OF BRAIN TISSUE IN THE DOG

Results are expressed in μg/g of tissue. Probability of no difference between the control and the drug-treated animals calculated by "t" test. The values represent means$\pm$standard deviation. The numerals in parentheses are concentrations of noradrenaline divided by the control value

Drug and dose/ kg body weight	No. of animals	Hypothalamus	Hippocampus	Frontal cortex	Midbrain
Control	15	0·919±0·104	0·162±0·074	0·129±0·013	0·285±0·075
Chlorpromazine 2 mg	5	1·988±0·695 (2·16) $P<0·001$	0·519±0·210 (3·2) $P<0·001$	0·154±0·078 (1·2) $P>0·05$	0·271±0·145 (0·95) $P>0·05$
Chlorpromazine 5 mg	5	2·178±0·469 (2·37) $P<0·001$	0·706±0·398 (4·36) $P<0·001$	0·321±0·008 (2·5) $P<0·001$	1·909±0·159 (6·7) $P<0·001$
Chlorpromazine 10 mg	10	0·502±0·206 (0·55) $P<0·001$	0·184±0·047 (1·14) $P>0·05$	0·115±0·034 (0·89) $P>0·05$	0·157±0·067 (0·56) $P<0·001$
Chlorpromazine 25 mg	5	1·023±0·205 (1·11) $P>0·05$	0·110±0·022 (0·68) $P<0·001$	0·040±0·007 (0·26) $P<0·001$	0·160±0·011 (0·56) $P<0·001$
Reserpine 2 mg	10	0·217±0·062 (0·24) $P<0·001$	0·039±0·021 (0·24) $P<0·001$	0·018±0·003 (0·14) $P<0·001$	0·035±0·006 (0·12) $P<0·001$

TABLE 2

ADRENALINE CONTENT OF BRAIN TISSUE IN THE DOG

Results are expressed in μg/g of tissue. Probability of no difference between the control and the drug-treated animals calculated by "t" test. The values represent means$\pm$standard deviation. The numerals in parentheses are concentrations of adrenaline divided by the control value.
* Less than 0·01 μg/g cannot be estimated with this method of bio-assay.

Drug and dose/ kg body weight	No. of animals	Hypothalamus	Hippocampus	Frontal cortex	Midbrain
Control	15	0·146±0·018	0·027±0·003	0·017±0·003	0·039±0·007
Chlorpromazine 5 mg	5	0·349±0·125 (2·39) $P<0·001$	0·280±0·037 (10·37) $P<0·001$	0·050±0·007 (3·0) $P<0·001$	0·526±0·094 (13·48) $P<0·001$
Chlorpromazine 10 mg	10	0·196±0·040 (1·34) $P<0·001$	0·087±0·046 (3·22) $P<0·001$	0·039±0·013 (2·0) $P<0·001$	0·118±0·119 (2·29) $P<0·001$
Reserpine 2 mg	10	0·059±0·038 (0·4) $P<0·001$	0·017±0·024 (0·63) $P>0·05$	<0·01* (0·0) $P<0·001$	0·012±0·007 (0·31) $P<0·001$

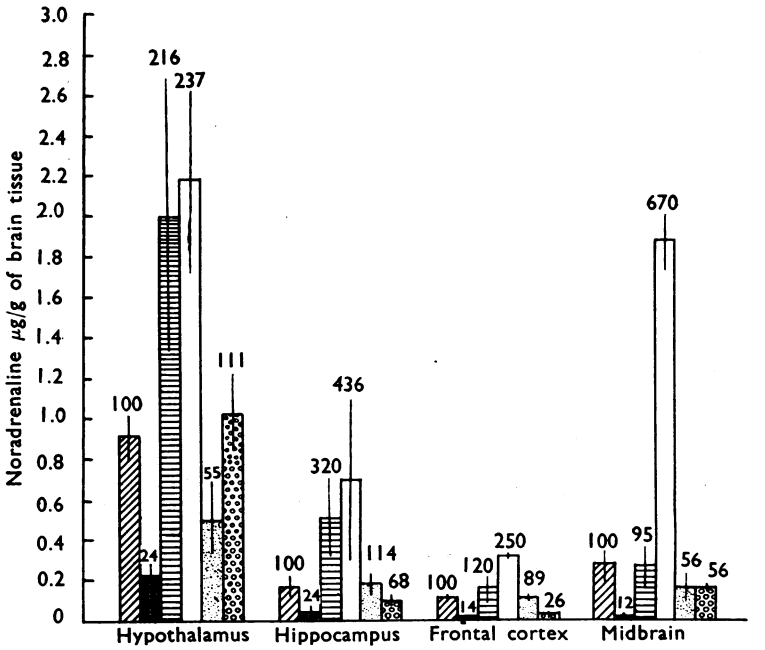

Fig. 1. Histogram showing the effect of reserpine and chlorpromazine on noradrenaline content of different parts of dog brain. Numerals over each bar show % of noradrenaline in relation to normal values (normal value=100).

I Standard deviation.
Without drug.
After reserpine 2 mg/kg.
After chlorpromazine 2 mg/kg.
After chlorpromazine 5 mg/kg.
After chlorpromazine 10 mg/kg.
After chlorpromazine 25 mg/kg.

In the control group, these two catechol amines were distributed unevenly, the amount being highest in the hypothalamus and lowest in the frontal cortex and the hippocampus. There was, however, no significant difference ($P>0.05$) in the relative proportions of these two catechol amines in different areas, noradrenaline content being seven to nine times as high as that of adrenaline.

Chlorpromazine

Noradrenaline. Chlorpromazine (2 mg/kg) raised the noradrenaline content in the hypothalamus and the hippocampus, while it had no significant effect ($P>0.05$) on that of the frontal cortex and the midbrain. With 5 mg/kg of chlorpromazine there was a marked rise of the noradrenaline in all the parts of the brain studied, the rise being very high in the midbrain (670%) and the hippocampus (436%). With 10 mg/kg of chlorpromazine, the noradrenaline concentration was significantly decreased ($P<0.001$) in the hypothalamus and the midbrain, while there was no significant change ($P>0.05$) in that of the frontal cortex and the hippocampus compared with controls. With 25 mg/kg of chlorpromazine there was a significant

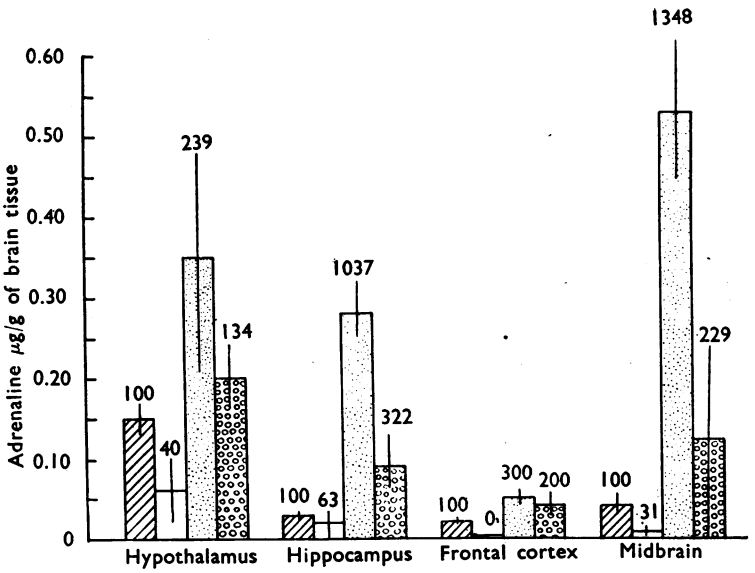

Fig. 2. Histogram showing the effect of reserpine and chlorpromazine on adrenaline content of dog brain. Numerals over each bar show % of adrenaline in relation to normal values (normal values=100).

I Standard deviation. After reserpine 2 mg/kg.
Without drug. After chlorpromazine 5 mg/kg.
After chlorpromazine 10 mg/kg.

reduction ($P<0.001$) in the noradrenaline content in all the parts of the brain studied except the hypothalamus, in which the change was not significant ($P>0.05$).

Adrenaline. Chlorpromazine, in doses of 5 and 10 mg/kg, raised consistently the adrenaline content of all the areas of the brain studied. The rise was more with 5 mg/kg, being very high in the regions of the midbrain (1,348%) and the hippocampus (1,037%).

Reserpine

Reserpine (2 mg/kg) decreased markedly the adrenaline and noradrenaline contents of all the parts of the brain studied. In all areas except the frontal cortex the decrease in noradrenaline was greater than in adrenaline. In general, the decrease in both the catechol amines after reserpine was more pronounced in the frontal cortex and the midbrain than in the other areas.

DISCUSSION

Our results show that chlorpromazine in the smaller doses raised the catechol amine content of the areas of the brain studied, the rise reaching its maximum with 5 mg/kg. Above this dose, the rise was less marked, while with 25 mg/kg there was actual diminution in noradrenaline content of all the areas except in the hypothalamus, in which the concentration did not differ from the control value.

Our results with 25 mg/kg of chlorpromazine on the noradrenaline content of the hypothalamus accord with the findings of Holzbauer & Vogt (1954) in the cat. Chlorpromazine produced a greater rise in the adrenaline than in noradrenaline content.

The effect of reserpine on the catechol amine content differed from that of chlorpromazine in two distinct ways. Firstly, reserpine caused depletion in both the catechol amines ; and secondly, the effect was usually greater for noradrenaline than for adrenaline. It is difficult to explain the mechanism by which small doses of chlorpromazine increased catechol amine concentration while the higher doses were less active or actually reduced the noradrenaline content. In this connexion it is of interest to note that Gey & Pletscher (1961) reported the inhibition of mitochondrial mono-amine oxidase by high concentration of chlorpromazine *in vitro* but could find no inhibition of cerebral mono-amine oxidase by chlorpromazine *in vivo* experiments.

Chlorpromazine affected the catechol amine content of the midbrain and of the hippocampus much more than that in other areas of the brain, while reserpine influenced the catechol amine content of the midbrain and the frontal cortex more than that in the other regions. Thus both the tranquillizing agents affected the catechol amine content of the midbrain containing the ascending reticular formations, though the effects were in opposite directions.

Our results serve to show how widely the effects of chlorpromazine on catechol amine content of various parts of the mammalian brain appear to vary, and suggest that further work is needed.

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