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ACTION OF ALPHA-METHYLDOPA ON THE PHARMACOLOGICAL AND BIOCHEMICAL EFFECT OF RESERPINE IN RATS AND MICE

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Abstract—400 mg/kg alpha-methyldopa i.p. inhibits the convulsion facilitating effect of 2,5 mg/kg reserpine i.p. in mice and rats. The effect of reserpine potentiating narcosis and decreasing spontaneous motility was not influenced by alpha-methyldopa. In animals pretreated with alpha-methyldopa reserpine does not decrease the norepinephrine content of the brain, but the serotonin level is as low as in animals given reserpine alone.

NACINA had demonstrated, that alpha-methyldopa (α-MD) is able to antagonize the reserpine induced catalepsy and convulsion facilitating effect in mice and the depletion of adrenal cholesterol and ascorbic acid in rats.[1] It is remarkable, that α-MD has a considerable sedative effect in mice[2,3] and awakes the reserpine sedated rats.[4,5]

In present study the effect of α-MD has been investigated on the convulsion facilitating, spontaneous motility decreasing and narcosis potentiating action of reserpine in connection with the brain amines level.

METHODS

The experiments were made on Wistar rats, 150–200 g, and mice, 18–23 g. Convulsions were brought about by metrazol. In the experiments with rats 60 mg/kg metrazol was administered subcutaneously and there was registered the number of animals with tonic extensor spasm. In mice, the convulsive threshold was determined by the slow intravenous metrazol infusion method of Orloff *and al.*[6] 0,5% metrazol solution was given 0,05 ml/10 sec till the tonic extensor convulsions were manifest.

The sleeping time was measured after the intravenous administration of thiopental both in rats and mice.

The motility was investigated in mice with the motimeter of Knoll.[7]

The norepinephrine (NE) determination was carried out according to Paasonen and Krayer[8] by blood pressure determination in cats.

Serotonin (5-HT) was extracted with acetone[9] and determinated on the rat's stomach.[10]

In all experiments 400 mg/kg α-MD was administered i.p. two hr before 2,5 mg/kg reserpine i.p. and four hr before the experiments.

RESULTS

The present experiments confirm the results of Nacina,[1] that α-MD inhibits the convulsion facilitating effect of reserpine in mice and the same could be demonstrated in rats. Table 1 and 2 display that α-MD has no anticonvulsive effect *per se*, but the convulsion facilitating effect of reserpine inhibits entirely.

TABLE 1. METRAZOL CONVULSION THRESHOLD IN MICE

Number of mice	Treatment	ml of 0·5% metrazol solution per 10 g
76		0·219 ± 0·063
30	reserpine	0·141 ± 0·06
19	α-MD	0·222 ± 0·086
19	α-MD + reserpine	0·232 ± 0·089

TABLE 2. METRAZOL CONVULSIONS IN RATS

Control	Reserpine	α-MD	α-MD + reserpine
4/10	6/10	2/10	1/10

TABLE 3. MOTILITY OF MICE

(The numbers represent the motimeter count during 30 min)

Number of mice	Treatment	Counts of motimeter
25		186 ± 77
14	α-MD	30 ± 27
16	reserpine	23 ± 31
13	α-MD + reserpine	13 ± 19

The further experiments show, that α-MD has a considerable sedative effect, which agrees with the results of Smith[2] and Leroy.[3] The sedative effect of 400 mg/kg α-MD is about the same as 2,5 mg/kg reserpine measured on the spontaneous motility of mice. When α-MD was administered before reserpine, the sedative effect was the same as when both drugs were given separately (Table 3). These results do not agree with those of Day and Rand[4] and Gunna and Honson[5] but it may be explained by the fact, that the authors administered α-MD after reserpine.

The results were similar when the influence of α-MD was investigated on the sleeping time, induced by thiopental in rats. As it is well known, reserpine potentiates the narcosis considerably, but α-MD has about eightfold so great an effect. When both drugs were administered together, the prolongation of sleeping time agreed with those caused by α-MD alone (Table 4).

On the basis of these results it seems that α-MD is able to separate the effects of reserpine. While the tranquilizing effects (decrease of spontaneous motility, narcosis potentiation) remain unaltered, the convulsion facilitating action is inhibited entirely. Therefore it seemed to be interesting to determine the action of reserpine on

the biogen amines content of the brain in the presence of α-MD. It is evident from Table 5. that when α-MD is administered before reserpine no NE decrease can be detected neither in mouse nor in rat brain, whereas the depletion of 5-HT takes place.

TABLE 4. THIOPENTAL NARCOSIS IN RATS

Number of rats	Treatment	Sleeping time (sec)
6		165 ± 25
6	reserpine	423 ± 258
6	α-MD	3417 ± 1253
6	α-MD + reserpine	3227 ± 1075

TABLE 5. NE AND 5-HT LEVEL OF BRAIN (γ/g)

Number of animals	Treatment	mouse NE	5-HT	rat NE
13		0·282 ± 0·044	0·745 ± 0·255	0·290 ± 0·029
5	reserpine	0·09 ± 0·037	0·299 ± 0·094	0·100 ± 0·072
8	α-MD	0·180 ± 0·055	0· 282 ± 0·134	0·159 ± 0·074
6	α-MD + reserpine	0·317 ± 0·075	0·258 ± 0·077	0·259 ± 0·05

DISCUSSION

The NE decreasing effect of α-MD comes about through depletion,[11] while it seems likely that the 5-HT decrease results from inhibition of 5-hydroxytryptophan decarboxylase.[12] This may be perhaps the explanation of the present results: the NE depleting effect of α-MD and reserpine is brought about by the same mechanism, but the action on the 5-HT level through a different mechanism. Carlsson and Linquist[13] stated that the α-MD goes through the same metabolic pathway in the brain as its physiological non-methylated analogue and α-methyldopamin and α-methylnorepinephrine are formed. According to the above mentioned authors the methylated amines are taken up by the specific storages and reserpine depletes these, too. So it may be perhaps supposed that α-MD competes with reserpine and therefore does not decrease the NE level of brain after reserpine in animals pretreated with α-MD.

Since the present experiments show, that α-MD inhibits the convulsion facilitating and brain NE decreasing effect of reserpine, but leaves its spontaneous motility, 5-HT decreasing and narcosis potentiating effect unaltered, it may be eventually concluded, that in the convulsion facilitating effect of reserpine the more important factor is the decrease of the brain NE level, while in the tranquilizing action the decrease of 5-HT level.

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