EFFECTS OF RUBIDIUM ON BEHAVIORAL RESPONSES TO METHAMPHETAMINE AND TETRABENAZINE

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Abstract—Different groups of mice were injected subcutaneously every other day with rubidium chloride at three doses (0.41(50), 1.23(150) and 3.69(450) meq/kg (mg/kg)) or with saline as a control for a period of 2-3 weeks. Rubidium administered acutely did not affect spontaneous locomotor activities, while it tended to increase the activities when administered repeatedly though the increase was not statistically significant. The methamphetamine-induced hyperlocomotor activities were potentiated in the rubidium groups as compared with those in the saline group, this effect of rubidium being increased with prolongation of repeated administrations. Monotonic decreases in ambulation after tetrabenazine were not significantly affected in the rubidium-treated animals though the decreases were sometimes preceded by slight increases and recovery from the decrement tended to be more rapid. After tetrabenazine in the rubidium-treated groups, incidences of catalepsy were increased and jumping behavior and Straub tail responses occurred in a few cases. The results suggest that rubidium potentiates the excitatory action of methamphetamine on spontaneous locomotor activities, as contrasted with inhibitory influence of lithium.

Rubidium and lithium, alkaline metals, have been proposed to have valuable therapeutic and prophylactic effects in manic-depressive psychosis; rubidium is principally effective in depressive states (1, 2) while lithium is effective mainly for manic states. In studies on animals, the behavioral activation caused by morphine is potentiated by rubidium in mice whereas it is antagonized by lithium (3). Thus rubidium and lithium presumably have opposite effects in all species.

Many studies have also been done on the neurochemical mechanisms underlying the affective disorders. The catecholamine hypothesis of affective disorders is that some, if not all, depressions are associated with an absolute or relative decrease in catecholamines, available at central adrenergic receptors sites, while elation, conversely, may be associated with an excess of such amines (4, 5). Associated with this hypothesis has been the proposal by one of the present authors (T.F.) that lithium modifies behavioral responses to methamphetamine and tetrabenazine and that these drugs act on the metabolism of endogenous brain catecholamines, inhibiting in particular the methamphetamine-induced excitation (6).

The present investigation was an attempt to study the effects of rubidium on behavioral responses induced by methamphetamine and tetrabenazine.

MATERIALS AND METHODS

Healthy ddY male albino mice obtained from the Kuroda Animal Laboratory (Kuma-
moto, Japan) were used. They were caged in groups of 10 and housed for a week before as well as throughout the experiment, and were always housed with their cagemates after injection or between behavioral test trials. Body weights were 15–17 g at arrival and 18–21 g at the start of the injections. The diet consisted of MF, Oriental Yeast Ltd.. The animals were permitted food and water ad libitum during the trials. All trials and breedings were carried out at an environmental temperature of 24±1 °C and a humidity of 50±10%.

The mice were divided randomly into 4 groups that were given injections of saline as control or of rubidium chloride in doses of 50 mg/kg (0.41 meq/kg), 150 mg/kg (1.23 meq/kg) or 450 mg/kg (3.69 meq/kg). One s.c. injection between 10:00 and 11:00 a.m. was given every other day for more than two or three weeks. Different groups of animals were used for each experiment. The number of mice used for each experiment is shown in the explanatory description for each figure and table.

Five measures of behavior were recorded.

Spontaneous locomotor activity: The activity was measured using the open-field method. The open-field chamber was 60 cm in diameter and 50 cm in height, and floor was divided into 19 blocks. A mouse was placed on the center of the floor and the activity was observed for 1 min. Two preliminary training trials were given at 30 min intervals in order to establish a relatively stable baseline prior to the test trials which began 30 min later. The short period for each test trial was chosen so as to measure drug effects at short time intervals after administration. Locomotor activity, ambulation, was expressed in terms of number of blocks traversed during 1 min.

Jumping behavior: Observation of the second measure of behavior has been referred to herein as a passive avoidance situation. Each mouse was placed in the center of an octagonal platform made of non-transparent plastic, 35 cm high and 32 cm in diameter. Whether or not a mouse jumped off the platform during 1 min period was recorded. This observation was repeated 3 times at intervals of 10 min. The jumping response was then calculated in terms of the percentage of animals which jumped in each group during the 3 trials.

Vertical jumping behavior: Each mouse was placed at the center of bottom floor of a cylinder-shaped open chamber constructed of transparent plastic, 7 cm in height and 20 cm in diameter. The behavior observed during each 1 min trial was whether or not a subject jumped vertically in such a way as to reach 7 cm or more above the floor of the chamber. This observation was repeated 3 times at intervals of 10 min. The vertical jumping response was then expressed in terms of the percentage of animals.

Catalepsy: Each mouse was hung on a small steel stick (2 cm in diameter) and kept in a 25 cm high horizontal position by the foreleg. The mouse which had sustained this posture for over 30 sec was estimated as positive reaction.

Straub tail: Mice whose tail remained raised in a vertical position for over 30 sec were classified as having a positive reaction.

Catalepsy and Straub tail responses were then expressed in terms of the percentage of animals in each group.
The drugs used were rubidium chloride (Kishida Chemical), methamphetamine hydrochloride (Dainippon Pharmaceutical) and tetrabenazine hydrochloride (Hoffman-La Roche). Rubidium chloride was dissolved in distilled water, sterilized, and administered s.c. in different 3 doses. Other drugs were also dissolved in distilled water and injected s.c.. Exactly 4 ml/kg of each drug was given at each injection. Methamphetamine (2.5 mg/kg) and tetrabenazine (5 mg/kg) were administered 24 hr after rubidium or saline.

Statistical tests of differences between experimental treatments were carried out using U test (p<0.05).

RESULTS

Effects of rubidium on increase in body weight

During chronic treatment, i.e., administration of rubidium or saline every other day for 16 days, body weight was increased similarly at 50 and 150 mg/kg in the rubidium treated animals but the increase in the weight was inhibited at 450 mg/kg, as compared with those in the saline-treated animals (Fig. 1).

Effect of rubidium on spontaneous locomotor activity

Ambulation was measured at several intervals after a single administration of rubidium or saline. As shown in Fig. 2, all treatments were followed by decreases in ambulation which were maximal at 3–5 hr and lasted for more than 7–9 hr, but
decreases observed with various doses of rubidium were not significantly different from those with saline.

During chronic treatment, ambulation was measured 24 hr after the 1st, 3rd, 5th, 7th, 9th, 11th administrations of rubidium or saline. As seen in Fig. 3, ambulations were not altered by treatment with saline. As compared with these ambulations in the saline group, the ambulations tended to be more numerous in the rubidium-injected animals though these differences in ambulation between the saline and rubidium group were not statistically significant.

**Effects of rubidium on methamphetamine-induced hyper-locomotor activity**

As shown in Fig. 4, methamphetamine, 2.5 mg/kg, injected 24 hr after the 3rd and 7th administrations of rubidium or saline, induced increases in ambulation which were maximal 60 min later and lasted over 3 hr. The methamphetamine-induced increases were significantly potentiated and durations of increase were more prolonged in the rubidium group than in the saline group, except when 50 mg/kg was given. This effect was the most pronounced at 150 mg/kg and the next at 450 mg/kg and was more marked with prolongation of the period and repeated administrations.

![Fig. 4. Influence of rubidium on spontaneous locomotor activity responses to methamphetamine](image)

**Effects of rubidium on behavioral responses to tetrabenazine**

Tetrabenazine, 5 mg/kg was injected 24 hr after the 3rd, 7th and 11th administrations of rubidium or saline, and ambulation, jumping behavior, vertical jumping behavior and Straub tail were determined at several time intervals. Tetrabenazine induced monotonic decreases in ambulation lasting for more than 3 hr in the saline group. In the rubidium group, this agent also elicited decreases in ambulation, but this was preceded by slight increases in some groups and recovery from the decrement in ambulation seemed to be more rapid, as summarized in Fig. 5. However, these differences in the effect of tetrabenazine
Fig. 5. Influence of rubidium on spontaneous locomotor activity responses to tetrabenazine. Tetrabenazine (5 mg/kg) was injected s.c. 24 hr after rubidium or saline. A; after the 3rd administration of RbCl or saline, B; after the 7th, C; after the 11th. Further explanations as in Fig. 4.

Fig. 6. Incidence of catalepsy after tetrabenazine in rubidium- or saline-treated mice. Each point indicates the percent animals with catalepsy. Further explanations as in Fig. 5.

between the saline and rubidium group were not significant.

Tetrabenazine also brought about a catalepsy. As shown in Fig. 6, incidences of catalepsy were increased after the 3rd and 7th injections of rubidium as compared with those in the saline groups. However, after the 11th administration, the incidence was extremely high even in the saline group.
TABLE 1. Jumping, vertical jumping behavior and Straub tail after tetrabenazine in saline- and rubidium-treated mice

| Drugs     | after 3rd Inj. | after 7th Inj. | after 11th Inj. |
|-----------|----------------|----------------|-----------------|
|           | J.  | V.J. | S.T. | J.  | V.J. | S.T. | J.  | V.J. | S.T. |
| Saline    | 0   | 0    | 0    | 0   | 0    | 0    | 0   | 0    | 0    |
| RbCl 50 mg/kg | 1   | 0    | 2    | 1   | 0    | 0    | 2   | 0    | 0    |
| RbCl 150 mg/kg | 1   | 0    | 3    | 2   | 0    | 1    | 2   | 0    | 1    |
| RbCl 450 mg/kg | 2   | 0    | 3    | 2   | 0    | 1    | 2   | 0    | 1    |

J.; jumping behavior, V.J.; Vertical jumping, S.T.; Straub tail. Each value indicates the number of mice among 8 showing such behavior. Tetrabenazine was administered s.c. 24hr after the 3rd, 7th and 11th injections of saline or rubidium chloride.

Jumping behavior and Straub tail occurred in a few cases in the rubidium group after injection of tetrabenazine as seen in Table 1, while such were not observed in the saline group. However, vertical jumping behavior was never observed in either the saline or rubidium groups.

DISCUSSION

Increases in body weight determined throughout the experiment were not affected when smaller doses of rubidium were given but were reduced when larger doses were given. Rubidium administered exogenously is reportedly distributed in various tissues including the brain (7-9) and is excreted very slowly (10, 11). Repeated administrations of rubidium in certain doses, therefore, result in exhibiting toxic effects such as a decrease in body weight (8, 12) and tetanic spasms or convulsion (12-15). The safety margin in the dosage of rubidium is narrow therefore if a toxic dose is given, the effects observed would be non-specific rather than specific. Accordingly, the effects observed herein with smaller doses of rubidium (50, 150 mg/kg) were generally interpreted as indicating specific actions whereas non-specific actions were considered when larger doses (450 mg/kg) were given.

In the present study on mice, a single s.c. administration of rubidium did not affect locomotor activity, but daily administrations elicited a slight excitation in locomotor activity. Rubidium chloride, administered i.p., 3 meq/kg/day, for 2 days, elicited no alterations in gross behavior of mice (3). Meltzer et al. (16) have reported that acute i.v. injection of rubidium chloride in the monkey produces phonation, struggling and facial twitching, and the most prevalent frequency (8-9 Hz) in EEG changes to 6-7 Hz and then increases to 10-11 Hz whereas chronic administrations produce hyperactive and aggressive behavior and a gradual increase is seen in the incidence of the higher frequencies. The behavior of the rats treated i.p. for 10 days with rubidium chloride, 0.6 meq/kg, was not apparently different from that of the saline-treated animals when compared within their home cages, but, upon handling, the rats become extremely irritable, displaying marked vocalization and aggressiveness toward the handler (17). Therefore, rubidium is thought to induce an excitation after repeated administrations.

Drug interaction between rubidium and methamphetamine or tetrabenazine in be-
behavioral actions has not been reported. The excitatory effect of methamphetamine on locomotor activity in our animals was potentiated by treatment with rubidium, and this effect was increased with prolongation of repeated administrations. Accordingly, the effect of rubidium appears to be opposite that of lithium reported previously by one of the present authors (T.F.) (6). Such is compatible with data that morphine activation is potentiated by rubidium but antagonized by lithium as reported by Carroll and Sharp (3) who proposed the involvement of central amines.

From the viewpoint of brain amine metabolism, amphetamine, related closely to methamphetamine in chemical structure and pharmacological action, releases amines, reduces amine uptake and inhibits monoamine oxidase activity in large doses (18-21), thereby increasing the availability of amines at the receptor site and inducing central excitation. With rubidium, greater amounts of neuronally stored monoamines are released to central adrenergic receptors, since turnover of brain amines are enhanced after rubidium treatment (17). As rubidium and methamphetamine are thought to act in a similar manner on brain amine metabolism, the biochemical effects on amine metabolism offer a plausible explanation for the behavioral synergism between rubidium and methamphetamine.

The inhibiting effect of tetrabenazine on locomotor activity was not significantly affected by treatment with rubidium, incidence of catalepsy was increased, and jumping behavior and Straub tail response appeared in a few cases; rubidium and lithium (6) did not necessarily exhibit opposite effects on behavioral response to tetrabenazine. Dopamine is present in a relatively high concentration in the extrapyramidal system of the brain in the dog and cat (22), and catalepsy may be the result of a depletion of dopamine in this area (23). Rauwolfia alkaloids such as reserpine and tetrabenazine may produce a catalepsy because of their depleting effect on brain amine, and catalepsy is also elicited by other neuroleptics, such as chlorpromazine which blocks amine receptors (24). Straub tail reportedly appears after morphine or after a large dose of tryptamine (25), and effects of these drugs may be mediated by central amines (26). The mechanism involved in the interaction between rubidium and tetrabenazine remains to be elucidated.

REFERENCES

1) Cade, J.F.J.: Med. J. Aust. 2, 349 (1949)
2) Dyson, W.L. and Mendelson, M.: Am. J. Psychiat. 125, 544 (1968)
3) Carroll, B.J. and Sharp, P.T.: Science 172, 1355 (1971)
4) Schildkraut, J.J.: Am. J. Psychiat. 122, 507 (1965)
5) Takahashi, R., Nagao, Y., Tsuchiya, K., Takamizawa, M., Kobayashi, T. and Kariya, T.: J. Psychiat. Res. 6, 185 (1968)
6) Furukawa, T., Ushizima, I. and Ono, N.: Psychoparmacol. Berl. 42, 243 (1975)
7) Olsson, K.A., Soremark, R. and Wing, K.R.: Acta physiol. scand. 77, 322 (1969)
8) Meltzer, H.L. and Lieberman, K.W.: Experientia 27, 672 (1971)
9) Bernstein, J.C. and Israel, Y.: J. Pharmacol. exp. Ther. 174, 323 (1970)
10) Kuhn, A.S., Dearborn, E.H., Burrows, B.A. and Relman, A.S.: Am. J. Physiol. 197, 1297 (1959)
11) Fieve, R.R., Meltzer, H.L. and Taylor, R.M.: Psychoparmacol., Berl. 20, 307 (1971)
12) Follis, R.H.: Am. J. Physiol. 138, 246 (1942)
13) Glendenning, B.L., Schrenk, W.G. and Parrish, D.B.: J. Nutr. 60, 563 (1956)
14) Relman, A.S., Lambie, A.T., Burrows, B.A. and Roy, A.M.: J. clin. Invest. 36, 1249 (1957)
15) Mitchell, P.H., Wilson, J.W. and Stanton, R.E.: J. gen. Physiol. 4, 141 (1921)
16) Meltzer, H.L., Taylor, R.M., Platman, S.R. and Fievet, R.R.: Nature 223, 321 (1969)
17) Stolk, J.M., Nowack, W.J., Barchas, J.D. and Platman, S.R.: Science 168, 501 (1970)
18) Farnebo, L.O.: Acta physiol. scand. Suppl. 371, 45 (1971)
19) Glowinski, J. and Axelrod, J.: J. Pharmacol. exp. Ther. 149, 43 (1965)
20) Rutledge, C.O.: J. Pharmacol. exp. Ther. 171, 188 (1970)
21) Svensson, T.H.: Arch. Pharmacol. 271, 170 (1971)
22) Phillis, J.W.: The Pharmacology of Synapse, p. 39, Pergamon Press, London and New York (1970)
23) Hornykiewicz, O.: Pharmacol. Rev., 18, 925 (1966)
24) Fog, R.L., Randrup, A. and Pakkenberg, H.: Psychopharmacol., Berl. 12, 428 (1968)
25) Tedeschi, D.H., Tedeschi, R.E. and Fellows, E.J.: J. Pharmacol. exp. Ther. 126, 223 (1959)
26) Furukawa, T., Sano, T., Kohno, Y., Koga, M. and Nagasaki, N.: Pharmacol. Biochem. Behav. 4, 419 (1976)