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Comparison of the Long-Term Cumulative Effects of Reserpine and Syrosingopine on General Activity

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PALFAI, T. AND T. J. WALSH. *Comparison of the long-term cumulative effects of reserpine and syrosingopine on general activity*. PHARMAC. BIOCHEM. BEHAV. **11**(5) 585–587, 1979.—Reserpine, but not syrosingopine, produced a cumulative decrease in general motor activity when administered once every 10 days for a total of 8 drug treatments. The maximum depression of activity was evident following the second reserpine administration. Following a 30 day drug-free period animals previously treated with reserpine still exhibited decreased motor activity. The data suggest that chronic reserpine treatment may result in long term, and perhaps permanent behavioral effects.

Rauwolfia alkaloids Mice Spontaneous activity Cumulative drug effects Reserpine Syrosingopine

THE rauwolfia alkaloid, reserpine, has pronounced effects on brain biochemistry and behavior. Among its many and complex pharmacological actions is its well documented ability to deplete the neural and organic stores of catechol- and indole- amines [1, 3, 8, 18, 19]. The behavioral consequences of reserpine include tremors, decreased spontaneous locomotor activity, reduced food intake and impaired memory formation [2, 7, 13, 14, 20]. Several investigators have suggested that the drug's effect on biogenic amines mediate these behavioral phenomena [4, 7, 12, 17].

For a number of years, it was considered that reserpine and its active metabolites were excreted before their biochemical and behavioral consequences became apparent. Recently, this "hit and run" explanation of the drug's action has been questioned. Maggiolo and Haley [10] reported that following an acute reserpine injection (4.0 mg/kg), a portion of the drug remained bound to mouse brain for at least 120 hr. Similarly, Giachetti and Shore [6] reported that following reserpine administration, the restoration of endogenous amine content, the rate of new granule appearance and the persistence of reserpine in neural tissue followed a similar time course. They suggested that a small amount of reserpine binds irreversibly to synaptic vesicles and that the recovery of aminergic function coincides with the formation of new synaptic granules.

If reserpine is bound irreversibly to synaptic vesicles following its repeated administration, one might show a long-term cumulative effect on behaviors that are mediated via biogenic amines. The available literature is unclear on this issue. Pirch [13], for example, reported that 0.5 mg/kg reserpine, administered for 10 consecutive days, produced a biphasic effect on activity in a circular runway. Activity decreased for the first 4 days followed by a rapid increase. By Day 10, the reserpine-treated animals were hyperactive relative to controls. A similar effect was reported by Segal and his colleagues [16] in an open field situation. In contrast, Pirch [13] found no behavioral recovery following chronic reserpine administration when using a rotorod situation. In fact, a dose-related cumulative impairment was apparent. Similarly, Kurtz [9], in our laboratory, found a long-term cumulative reserpine effect on activity, food and water intake.

Since reserpine is clinically still prescribed as an antihypertensive agent [11,15] and in light of Giachetti and Shore's hypothesis, it is important to elucidate whether long-term, cumulative and/or, perhaps, permanent behavioral effects occur following its repeated administration. In the present study, we investigated the effect of chronic reserpine and syrosingopine administration on general activity in mice. We sought to determine whether reserpine or its peripherally active analogue, syrosingopine, would produce cumulative effects on activity if administered once every 10 days, for a total of 8 drug administrations.

METHOD

Animals

Adult male albino mice bred from CD-1 stock in our animal colony were used. The animals were housed in groups of four in plastic cages in a temperature and humidity-controlled environment. Food and water were continuously available in the home cage and a 12-hr light/dark cycle was in effect. The mice at the beginning of testing weighed between 30 and 40 g and were approximately 70 days old.

Apparatus

A Lehigh Valley Electronics Model 1497 activity monitor

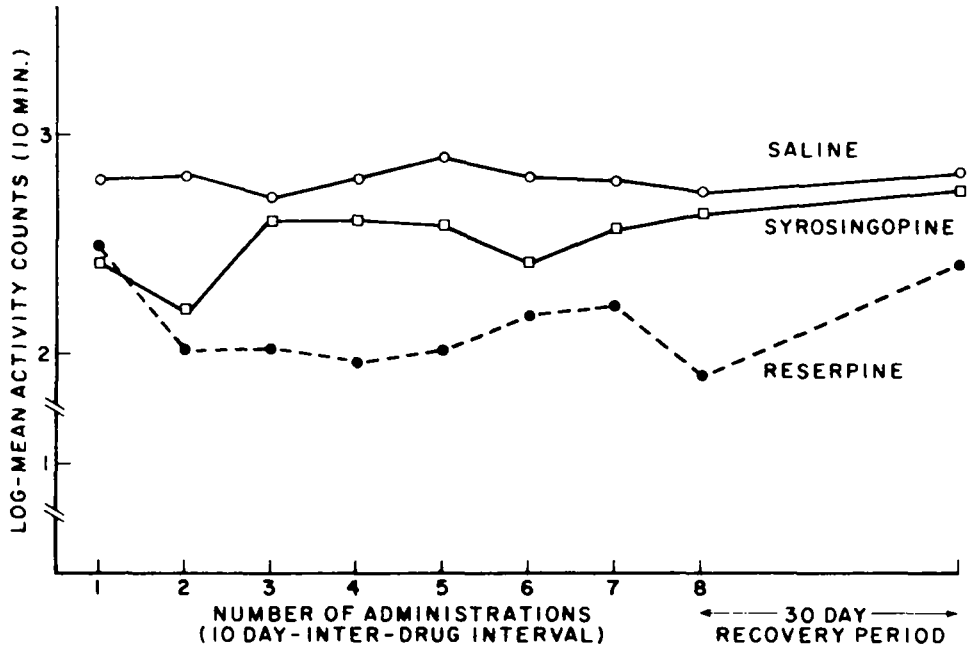

FIG. 1. Mean 10 min activity scores (converted to logs) for the 8 drug administrations and following the drug-free recovery period. N=6 in all groups.

was used to measure general activity. The apparatus consisted of a circular chamber (45 cm in dia.×42 cm in height) that had 12 equidistant photoelectric cells positioned 2.54 cm off the floor. Each time the animal interrupted the continuity of a photo-beam, an electronic counter was activated. The index of activity was the number of activity counts accumulated by an animal during a 10-min test period.

Procedure

Animals were administered 2.5 mg/kg reserpine (Serpasil, Ciba), syrosingopine (Singoserp, Ciba) or saline intraperitoneally (IP) 2 hr prior to each activity testing session. The activity test consisted of placing each mouse into the center of the chamber and allowing him 10 min of free exploration. Activity was recorded every 10 days for 80 days (i.e., 8 drug administrations). Following a 30-day drug-free period, the animals were again tested for activity but this time all animals received only a saline injection.

RESULTS AND DISCUSSION

The results are shown in Fig. 1. Two-way analysis of variance (ANOV) using repeated measures has resulted in a significant Treatment effect, $F(2,15)=5.34$, $p<0.02$, and a significant Treatment×Tests interaction, $F(14,105)=8.03$, $p<0.001$. The Test effect was not significant, $F(7,105)=0.17$, $p>0.10$. The result of this analysis suggests that the drug treatments had a significant effect on motor activity. Compared to saline controls both the reserpine, $t(10)=3.40$, $p<0.01$, and syrosingopine, $t(10)=3.90$, $p<0.01$, groups had reduced motor activity after the first drug administration. With repeated administration, behavioral tolerance seemed to develop to the effects of syrosingopine. By the third drug administration, syrosingopine-treated animals were not significantly different from the saline controls, $t(10)=1.10$, $p>0.05$. In contrast, no behavioral tolerance was apparent with reserpine, the drug produced a cumulative effect on locomotor activity. To examine this effect, a one-way ANOV was performed on the mean activity scores for the reserpine group during each of the eight Test sessions; this was followed by post-hoc comparisons with a Duncan Multiple Range Test [5].

The one-way ANOV across the reserpine treatment means indicated a significant time effect, $F(7,40)=2.30$, $p<0.05$. Multiple comparisons with the Duncan Multiple Range Test indicated that general activity following the first reserpine administration was significantly different from activity during the subsequent test sessions ($p<0.05$ for all comparisons). The level of activity was not different among tests 2–8. The results of this analysis suggest that reserpine depresses activity maximally following its second administration. The extent of this depression, however, is not altered after subsequent drug treatments. The explanation of this finding might be found in terms of a reversed ceiling effect. Further research is required to test this hypothesis.

Finally, following the 30-day drug-free period, the animals in the saline and syrosingopine groups showed comparable activity levels when tested again in the activity apparatus. The animals that received 8 reserpine treatments over an 80-day period, had still not recovered their normal activity level after 30 days. These data suggest that chronic reserpine administration might produce permanent effects on general activity.

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