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BRIEF COMMUNICATION

Effects of Salsolinol, a Tetrahydroisoquinoline Alkaloid, on Multiple Schedule Performance in Rats[1]

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HYMOWITZ, N. AND H. E. BREZENOFF. *Effects of salsolinol, a tetrahydroisoquinoline alkaloid, on multiple schedule performance in rats.* PHARMAC. BIOCHEM. BEHAV. 8(2) 203–205, 1978. – Rats were trained to lever press under a multiple fixed-ratio fixed-interval schedule of food reinforcement. Intracerebroventricular injections of salsolinol (1–methyl–6,7–dihydroxytetrahydroisoquinoline), a condensation product of dopamine and acetaldehyde, caused a dose-related decrease in fixed-ratio responding over a dosage range of 15–120 μg. In contrast, fixed-interval responding was only reduced at the 120 μg dose and was increased in two of the animals after injection of 15–30 μg of salsolinol.

Intraventricular injection Salsolinol Tetrahydroisoquinoline alkaloids Operant behavior

TETRAHYDROISOQUINOLINE (TIQ) alkaloids are condensation products of a catecholamine and an aldehyde. They are taken up and stored in brain synaptosomes [1] and sympathetic nerve terminals [2], and can be released from their storage sites by acetylcholine [3], or electrical stimulation [4]. It has been suggested that these alkaloids form in the central nervous system during ethanol intoxication and may contribute to either the pharmacological effects of, or tolerance to, alcohol [5, 6, 7]. Salsolinol (1–methyl–6, 7–dihydroxy–TIQ), which is formed by condensation of dopamine and acetaldehyde, has been demonstrated in human urine [8] and rat brain [9] following administration of ethanol.

Previous work in this laboratory has shown that injection of TIQ alkaloids into the cerebral ventricles of rats causes a fall in body temperature, apparently due to the release of brain catecholamines [10]. The present experiment extends the analysis of these alkaloids to include the effects on behavior of intracerebroventricular (ICV) injections of salsolinol. This route of administration was used due to the probable poor penetration of the TIQ alkaloids through the blood-brain barrier and in order to restrict the drug action to the central nervous system. Since relatively little is known about the doses of salsolinol which affect behavior, a within animal design [11] was used in which each animal was exposed to a wide range of doses. Moreover, responding in the rats was studied under a multiple fixed-interval fixed-ratio schedule of food delivery. In this manner, it was possible to compare within the same animal the effects of salsolinol on lever pressing under two food reinforcement schedules.

METHOD

Four male, albino, Sprague-Dawley rats (S1–S4) served as subjects. They were housed individually and maintained at 80% of their initial free-feeding weight of 320–350 g.

Under ketamine anesthesia, a 22 gauge stainless steel guide for intracerebroventricular (ICV) injections was directed towards the lateral ventricle through a burr hole in the skull. The guides were permanently fixed to the skull with dental cement and plugged with a removable stillette.

The experiments were performed in a Grason-Stadler sound attenuated operant chamber equipped with a white-noise generator. Animal 1 was studied under a multiple fixed-ratio 25, fixed-interval 50 sec (mult FR 25, FI 50-sec) schedule of reinforcement (0.045 g food pellets) while S2, S3 and S4 were studied under mult FR 20, FI 55-sec food delivery. With fixed-ratio schedules, the delivery of food is dependent upon the emission of a fixed number of responses. For the fixed-interval schedule, the first lever press after a fixed period of time had elapsed produced the food pellet. Each component lasted six min and alternated throughout the session for a total of eight components. Three lights in the chamber were on during the fixed-ratio component and off during the fixed-interval component. The experiments were performed five days per week and the starting component was alternated daily.

Salsolinol HBr (K and K Laboratories, Plainview, NY) was dissolved in saline and injected ICV in a volume of 10 μl via a 28 gauge injection cannula inserted through the guide. Injections were given twice per week and were administered during a 30 sec interval 2 min prior to the start of the session. Salsolinol was administered in both

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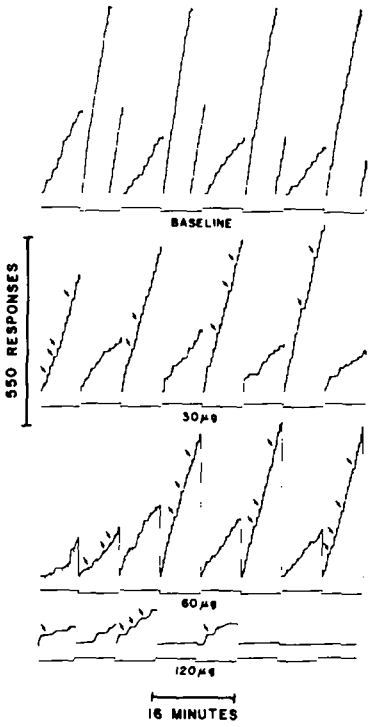

FIG. 1. Cumulative records for rat S1 following ICV injection of saline (baseline) or salsolinol (30, 60 or 120 μg) under a multiple FR 25, FI 50-sec schedule. The FR components are indicated by the downward deflection of the event pen, lever presses, by the vertical movement of the response pen, and pellets, by the downward deflection of the response pen. The response pen reset to the bottom of the scale after each component or after 550 responses. The arrows show the increase in postpellet pausing.

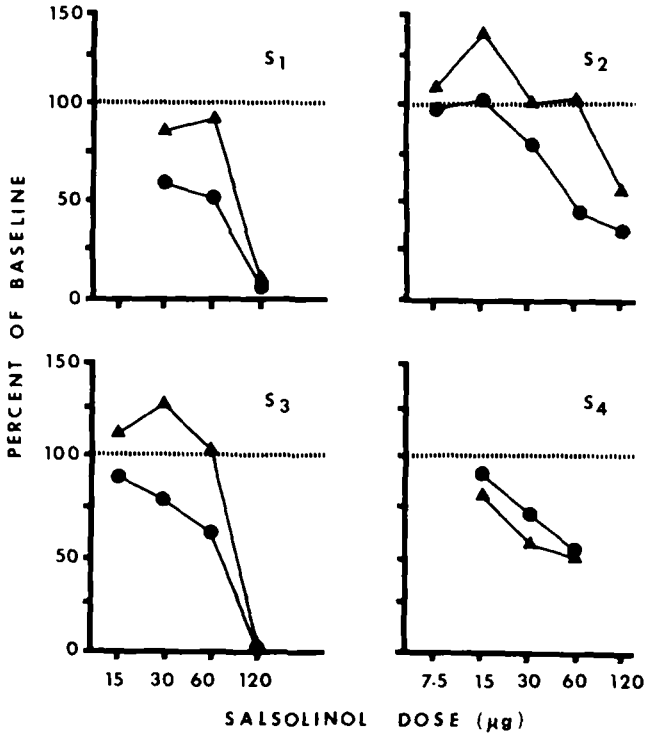

FIG. 2. The effect of salsolinol on lever pressing, expressed as the percent of baseline responding rate, under the fixed-ratio (circles) and fixed-interval (triangles) schedules. Each point represents the mean of 2 experiments. Control mult FR FI responding rates were: S1 = 3026 ± 68/730 ± 39; S2 = 2365 ± 60/1376 ± 40; S3 = 2110 ± 54/1036 ± 65; S4 = 491 ± 12/530 ± 23.

ascending and descending doses so that most doses were tested at least twice in each rat. Injection of saline (10 μl) did not significantly alter control responding rates.

RESULTS

Baseline

Under fixed-ratio food delivery, S1, S2 and S3 maintained a high steady rate of responding with little postpellet pausing. During the fixed-interval schedule, they maintained a consistent scalloped pattern of responding with the rate of responding increasing towards the end of each inter-pellet interval. A typical record for S1 is shown in Fig. 1. In addition to the differences in the pattern of responding between the two components, S1, S2 and S3 also responded at a much more rapid rate during the fixed-ratio component (Figs. 1 and 2). Animal 4, on the other hand, responded at a relatively low rate in both components. Analysis of the cumulative records of S4 revealed characteristic scalloped patterns of fixed-interval responding in both components throughout the session, indicating poor control of responding by the fixed-ratio schedule.

Effects of Salsolinol on Operant Responding

Intracerebroventricular injections of salsolinol (15–120 μg) caused a dose-related decrease in the rate of fixed-ratio responding. Doses of salsolinol which reduced fixed-ratio responding in S1, S2 and S3 by up to 50%, however, either enhanced slightly or did not affect fixed-interval responding. At the higher doses, responding for all of the animals was markedly reduced in both components (Fig. 2). Animal 4, who showed no baseline differences in the rate or pattern of responding under either schedule, failed also to reveal differential sensitivity to salsolinol.

Figure 1 shows representative records for S1 under each dose of salsolinol. At 30 and 60 μg, the reduction of fixed-ratio responding was due primarily to an increase in the frequency and duration of postpellet pausing. The rate of lever pressing (running rate), once initiated, was not noticably affected. At 20 μg, the running rate also was slowed and disrupted.

Responding of S2 and S3 under the fixed-interval schedule increased at the 15–30 μg doses of salsolinol, while the responding of S1 at the 30 and 60 μg doses was not significantly altered (Fig. 2). (Lower doses were not administered to S1 due to clogging of the cannula.) The cumulative records for Animals 2 and 3 reveal an increase in the number of responses which occurred in the early portions of the inter-pellet interval. At 120 μg, fixed-interval responding was severely impaired in all of the animals. Despite this impairment, the animals were quite active and readily accepted postsession feeding.

DISCUSSION

The effects of salsolinol on responding in the rat is a function of the dose of drug and schedule of food delivery. Doses of salsolinol which reduced responding maintained under the fixed-ratio schedules either slightly enhanced

fixed-interval responding in two of the animals or did not affect fixed-interval responding in another animal.

Since responding in one component of the multiple schedule was relatively unaffected at doses which decreased responding in the other component, it is unlikely that the reduction of responding was due to the effect of the drug on the animals' underlying motivational state, motoric impairment, or failure to generalize across drug and non-drug states (i.e., dissociation). Certain central nervous system stimulants such as amphetamine [12,13] and imiprimine [14,15] as well as depressants such as chlorpromazine [16] tend to disrupt high rates of behavior more than behavior maintained at a low rate. It appears as if salsolinol shares this rate-dependent effect. Since there is evidence that TIQ alkaloids may play some role in either the pharmacological effects of, or tolerance to, alcohol [5, 6, 7], and that ICV injections of related compounds (tetrahydropapaveroline) lead to excessive alcohol consumption in animals [17,18], further analyses of the effects of salsolinol on behavior appears warranted.

Tetrahydroisoquinoline alkaloids may contribute to either the pharmacological effects of, or tolerance to, alcohol. Relatively little is known about the effects of these alkaloids on behavior. The present experiment studied the effects on multiple schedule performance in rats of intracerebroventricular injections of salsolinol. In three of the four animals studied, doses of salsolinol which reduced lever pressing maintained under a fixed-ratio schedule either increased or had no effect on responding maintained under a fixed-interval food schedule. At the higher dose, responding in both components of the multiple schedule was markedly reduced.

REFERENCES

1. Heikkila, R., G. Cohen and D. Dembiec. Tetrahydroisoquinoline alkaloids: Uptake by rat brain homogenates and inhibition of catecholamine uptake. *J. Pharmac. exp. Ther.* **179**: 250–258, 1971.
2. Cohen, G., C. Mytilineou and R. E. Barrett. 6,7–Dihydroxytetrahydroisoquinoline: Uptake and storage by peripheral sympathetic nerve of the rat. *Science* **175**: 1269–1272, 1972.
3. Greenberg, R. E. and G. Cohen. Tetrahydroisoquinoline alkaloids: Stimulated secretion from the adrenal medulla. *J. Pharmac. exp. Ther.* **184**: 119–128, 1973.
4. Mytilineou, C., G. Cohen and R. Barrett. Tetrahydroisoquinoline alkaloids: Uptake and release by adrenergic nerves in vivo. *Eur. J. Pharmac.* **25**: 390–401, 1974.
5. Cohen, G. and M. Collins. Alkaloids from catecholamines in adrenal tissue: Possible role in alcoholism. *Science* **167**: 1749–1751, 1970.
6. Cohen, G. Reactions of catecholamines with acetaldehyde to form tetrahydroisoquinolines. In: *Advances in Mental Science III. Biological Aspects of Alcohol*, edited by M. K. Roach, W. M. McIssac and P. J. Creaven. Austin: University of Texas Press, 1971, p. 267.
7. Yamanaka, Y., M. J. Walsh and V. E. Davis. Salsolinol, an alkaloid derivative of dopamine formed in vitro during alcohol metabolism. *Nature* **227**: 1143–1144, 1970.
8. Sandler, M., S. B. Carter, K. R. Hunter and G. M. Stern. Tetrahydroisoquinoline alkaloids: In vivo metabolites of L–dopa in man. *Nature* **243**: 439–443, 1973.
9. Collins, M. A. and M. D. Bigdeli. Tetrahydroisoquinolines in vivo: I. Rat brain formation of salsolinol, a condensation product of dopamine and acetaldehyde, under certain conditions during ethanol intoxication. *Life Sci.* **16**: 585–602, 1975.
10. Brezenoff, H. E. and G. Cohen. Hypothermia following intraventricular injection of a dopamine-derived tetrahydroisoquinoline alkaloid. *Neuropharmacology* **12**: 1033–1038, 1973.
11. Sidman, M. *Tactics of Scientific Research.* New York: Basic Books, 1960.
12. Dews, P. B. Studies on behavior. IV. Stimulant actions of methamphetamines. *J. Pharmac. exp. Ther.* **122**: 137–147, 1958.
13. McMillan, D. E. Effects of d-amphetamine on performance under several parameters of multiple fixed-ratio, fixed-interval schedules. *J. Pharmac. exp. Ther.* **167**: 26–33, 19699.
14. Dews, P. B. A behavioral output enhancing effect of imipramine in pigeons. *Int. J. Neuropharmac.* **1**: 265–272, 1962.
15. Smith, C. B. Effects of d-amphetamine upon operant behavior of pigeons: Enhancement by reserpine. *J. Pharmac. exp. Ther.* **146**: 167–174, 1969.
16. Leander, J. D. and D. E. McMillan. Rate-dependent effects of drugs. I. Comparisons of d-amphetamine, phenobarbital and chlorpromazine on multiple and mixed schedules. *J. Pharmac. exp. Ther.* **188**: 226–239, 1974.
17. Myers, R. D. and C. L. Melchior. Alcohol drinking: Abnormal intake caused by tetrahydropapaveroline (THP) in brain. *Science* **196**: 554–556, 1977.
18. Melchior, C. L. and R. D. Myers. Preference for alcohol evoked by tetrahydropapaveroline (THP) chronically infused in the cerebral ventricle of the rat. *Pharmac. Biochem. Behav.* **7**: 19–35, 1977.