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# Characteristics of Reserpine-Induced Suppression of NaCl Solution Intake in Rats[1]

HISASHI KURIBARA,[2] JOHN L. FALK[3] AND MAISY TANG

*Department of Psychology, Busch Campus, Rutgers University, New Brunswick, NJ 08903*

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KURIBARA, H., J. L. FALK AND M. TANG. *Characteristics of reserpine-induced suppression of NaCl solution intake in rats.* PHARMACOL BIOCHEM BEHAV **28**(2) 209–211, 1987.—Effects of single and repeated administration of reserpine on time-limited drinking of a hypertonic (1.5% w/w) NaCl solution were investigated in rats to assess whether this drug possesses anxiolytic action. Rats adapted to a 23-hr water-deprivation schedule with a free-feeding regimen were allowed a daily 1-hr water rehydration session. In the single-administration experiment, reserpine (0.1, 0.2 and 0.4 mg/kg, IP) was administered to rats at 15 min or 23 hr before a drinking session, where the fluid available was 1.5% NaCl solution. Drug was administered every 7th day. In the repeated-administration experiment, reserpine (0.1 mg/kg/day) was injected daily for 10 days 15 min before each drinking session. The fluid available was water on the first 9 days and NaCl solution on the 10th day. Reserpine suppressed NaCl solution intake when it was singly administered at 15 min before the rehydration, whereas no significant change in the fluid intake occurred when it was administered 23 hr before drinking, even though rats showed ptosis in response to 0.2 and 0.4 mg/kg doses. Tolerance developed to the suppressing effect of repeated administration of reserpine on fluid intake, although ptosis and sedation continued and body weights decreased. Tolerance was almost complete after 11 days. The results suggest that reserpine does not have an anxiolytic effect.

Reserpine NaCl intake Fluid intake Repeated administration Tolerance Anxiolytic

IT has been demonstrated that anxiolytic benzodiazepines and barbiturates increase the intake of hypertonic and other NaCl solutions when rats are subject to a time-limited drinking schedule [7–9, 16, 17]. It was originally hypothesized that the taste of hypertonic NaCl solution might be an aversive stimulus which suppresses fluid consumption in much the same way that contingent electric shock suppresses behavior in the conflict situations developed by Geller and Seifter [10] and modified by Vogel *et al.* [18]. The anxiolytic action of drugs is detectable in all these situations as an increase in the suppressed behavior, although they also selectively increase the intake of highly-acceptable foods and fluids [5].

Early research with reserpine indicated that it might possess punishment-attenuating properties [11] as well as alleviating responding suppressed by the conditioned emotional response procedure [3,14]. Reserpine is of interest since, except for occasional weak effects, it is the only neuroleptic reported to exhibit antipunishment properties.

## METHOD

### *Animals*

Ten adult, male, Holtzman rats (Madison, WI) were used. They were individually housed in standard stainless-steel cages in a temperature-controlled (22±1°C) room with a 12-hr light-dark cycle (lights on 0700–1900 hr). The experiment was started when the average body weight was 360 g (range: 353–370 g).

### *Drug*

Reserpine (Sigma Chemical, St. Louis, MO) was dissolved in a 1% acetic acid vehicle immediately before use. The drug was injected intraperitoneally (IP) according to the schedule described below. The concentration of each drug solution was adjusted so that the volume injected was always constant at 1 ml/kg.

### *Procedure*

The basic experimental procedure was similar to that described previously [8,9]. Briefly, all rats were adapted to a 1-hr time-limited water (distilled) drinking schedule which started at 1100 hr and ended at 1200 hr every day. Water was available from a stainless-steel drinking spout (Ancare, TD-300) attached to a 100-ml Nalgene calibrated cylinder. Immediately before the start of water presentation (rehydration), all rats were weighed and food (Purina Lab Chow,

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[2]On leave from: Division for Behavior Analysis, Behavior Research Institute, Gunma University School of Medicine, Maebashi, Japan.
[3]Requests for reprints should be addressed to John L. Falk.

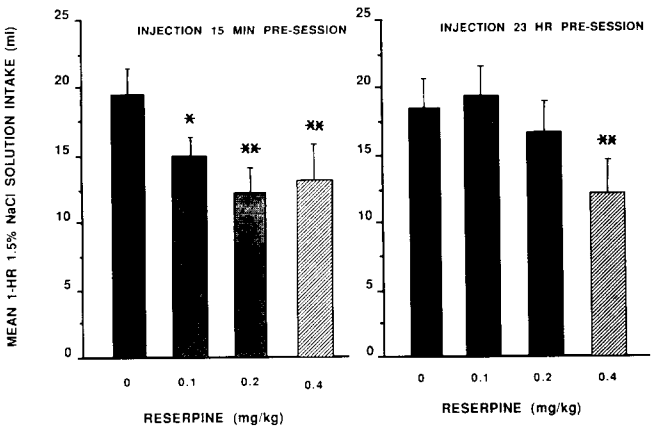


FIG. 1. Mean (+S.E.) intake (ml) of 1.5% NaCl solution during 1-hr rehydration session as a function of a pre-session reserpine dose (IP) given either 15 min (left panel) or 23 hr (right panel) before drinking. *=$p<0.05$; **=$p<0.01$.

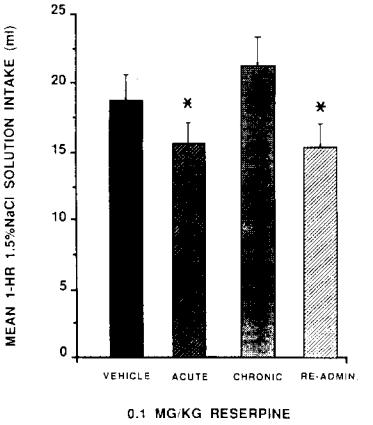


FIG. 2. Mean (+S.E.) intake (ml) of 1.5% NaCl solution during 1-hr rehydration session as a function of acute, chronic (10th day) and readministration (after 10 days of drug discontinuation) dose of 0.1 mg/kg reserpine (IP) 15 min pre-session. *=$p<0.05$ (chronic vs. acute and readministration).

pelleted) was removed from the cages. At the end of the rehydration, fluid intakes of individual rats were recorded and the drinking tubes were removed. Food was then replaced. Thus, food was freely available except during the rehydration period. After daily fluid intake had stabilized, the reserpine acute dose-response function was determined (0.0, 0.1, 0.2 and 0.4 mg/kg). Injections were administered intraperitoneally 15 min pre-session every 7th day with dose order randomized among rats. On injection days, a 1.5% (w/w) NaCl solution was substituted for water as the drinking fluid. After the completion of this dose-effect determination, an identical series of doses was administered immediately post-session every 7th day and the intake of 1.5% NaCl solution was evaluated 23 hr later by presentation of the usual 1-hr drinking session. Upon completion of this second dose-effect relation, a repeated-administration series was begun. Reserpine was injected (IP) daily at 0.1 mg/kg for 10 days 15 min before each drinking session. Water was the fluid available for the first 9 days, while 1.5% NaCl solution was the 10th day session fluid. Reserpine treatment was then terminated and water was available during the next 10 drinking sessions; 1.5% NaCl solution was given on the 11th session, preceded by 15 min with a readministration of a 0.1 mg/kg dose of reserpine.

## RESULTS

Figure 1 shows the mean fluid intakes of 1.5% NaCl solution after the acute administration of 0, 0.1, 0.2 and 0.4 mg/kg doses of reserpine 15 min (left panel) or 23 hr (right panel) before the 1-hr drinking session. An overall analysis of variance indicates that reserpine significantly decreased fluid intakes in a dose-dependent manner, $F(3,27)=5.445$, $p<0.01$, when it was administered 15 min before rehydration. Comparisons between individual means using the Newman-Keuls method reveal that the mean intake following vehicle injection was significantly different from that following reserpine administration ($p<0.05$ for the 0.1 mg/kg dose and $p<0.01$ for the 0.2 and 0.4 mg/kg doses).

A significant change in fluid intake was also obtained when rats were treated with reserpine at 23 hr before the rehydration, $F(3,27)=7.811$, $p<0.01$. Individual comparisons between treatment means, however, show that only the intake for the 0.4 mg/kg reserpine dose ($p<0.01$) is significantly decreased.

No marked change in water intake was observed during the initial 9 days of chronic reserpine administration. Figure 2 shows the mean intake of 1.5% NaCl solution for 9 rats in response to a 0.1 mg/kg reserpine dose before (acute) and after repeated administration (10th day), and on the 11th day after termination (readministration) of the chronic, daily drug doses. Only data from 9 animals are included in this phase of the analysis since one rat was excluded owing to illness. An overall analysis of variance across the four conditions yielded significance: $F(3,24)=4.703$, $p<0.05$. Post-mortum analysis using the Newman-Keuls test revealed that the chronic effect was significantly different from both the acute and readministration values ($p<0.05$).

Gross observation revealed that acute administration of reserpine had little effect at 1–2 hr. At 3–4 hr after 0.2 and 0.4 mg/kg reserpine a ptosis appeared. It was more marked on the next day and persisted for 2–4 days. Although acute administration of reserpine at 0.1 mg/kg produced no observable symptoms, the repeated administration of the same dose progressively produced a ptosis, sedation and a minor decrease in body weight (about 5.5 g by the 10th administration day). After reserpine termination, 4–7 days were required for animals to return to condition that appeared normal.

## DISCUSSION

The present experiment demonstrated that acute doses of reserpine, unlike proven anxiolytic agents, suppressed the intake of NaCl solution in water-deprived rats. Drugs having anxiolytic action selectively increase the intake of various NaCl solutions under these circumstances [5, 7–9, 16, 17]. If an increase in NaCl solution drinking by rehydrating rats is a valid indicator of anxiolytic action, then reserpine is not an anxiolytic agent. Geller and his associates [11], using a standard operant punishment-attenuation situation with rats, reported a positive result with reserpine. Since chronic, post-session injection of reserpine was required for the punishment-attenuation effect to manifest, this fact guided the selection of a similar, repeated-administration regimen in

the second phase of the present study. Similarly, using the conditioned emotional response technique as an indicator of anxiolytic effect, both Brady [3,4] and Sidman [14] found that chronic reserpine administration produced increases in the suppressed level of responding in both rats and rhesus monkeys. However, the present experiment yielded no indication that reserpine increased the level of NaCl solution ingestion. Studies using place punishment [1] and punishment by electrified-water-ingestion [2] techniques also failed to find an anxiolytic action for reserpine.

The investigation of other neuroleptic drugs as possible anti-anxiety agents has yielded fairly consistent results. Using a punishment technique, Aron *et al.* [1] found no neuroleptic agent that was effective, including both the acute and chronic administration of reserpine. The model which uses the attenuation, by a drug, of suppression produced by punishment (Geller-Seifter technique) usually yields negative results for neuroleptics such as chlorpromazine and promazine [10, 12, 15]. However, some positive results have been reported for chlorpromazine [13] and for trifluoperazine [6] using this technique, as well as for chlorpromazine using the electrified-water-ingestion method [2]. In general, those positive results which have occurred with neuroleptic agents are of small magnitude over a narrow dose range.

The decreased NaCl solution intake produced by acute doses of reserpine was presumably due to some aspect of the release of catecholamines or 5-HT from central neuronal storage sites. The tolerance to the suppressive effect of reserpine on NaCl solution intake which developed with repeated administration of the drug may be attributable to the known recovery from the initial, acute inhibition of tyrosine hydroxylase activity which occurs when chronic reserpine treatment is instituted [19].

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