

Effects of chlorpromazine in rats trained to discriminate between 2 and 22 hr food deprivation

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Introduction

Chlorpromazine, a typical antipsychotic, has been shown to have varying effects on food intake. Chlorpromazine is a dopamine antagonist that blocks several dopamine receptors (including D1 and D2). Previous research indicated chlorpromazine (5.0mg/kg) may affect food intake in two time phases. In the first phase, which is up to 2 hours post-injection, food intake is initially suppressed. Beyond 2 hours, food intake is significantly enhanced above the control level. There was a larger increase in food intake between 2-7 hours but was still increased up to 24 hours post-injection. In the present investigation, we evaluated the effects of chlorpromazine in our food-deprivation discrimination paradigm that may serve as an animal model of 'hunger.' We assessed the ability of chlorpromazine to alter the discriminative stimulus effects of 22 hours acute food deprivation. Results may lead to a better understanding of the mechanisms behind hunger and to advancing the pharmacological treatment of eating-related disorders.

Method

Subjects and apparatus

- Male Sprague-Dawley rats were housed in individual cages in a room with 12:12 light/dark cycle (lights on at 8:00 a.m.) and given continuous access to rodent chow (Harlan Teklad) and water unless noted.
- 45-mg food pellets (Bioserve F#0021) were delivered as reinforcers in standard two-lever operant chambers (Med-Associates).

Drug

- Chlorpromazine (0.32-3.2mg/kg) was dissolved in 0.9% saline and administered i.p.

Behavioral training

- Correct lever presses, left lever presses following 22 hr food deprivation and right lever presses following 2 hr deprivation, were reinforced with food pellet delivery under FR-15.
- Incorrect lever presses resulted in an 8 second period of darkness.
- Each training session included two response cycles that ended after five food reinforcers were earned or 5 minutes elapsed, whichever occurred first.
- Training continued until subjects emitted greater than 80% condition-appropriate responses both prior to the first reinforcer delivery for each training cycle and for the complete training session.

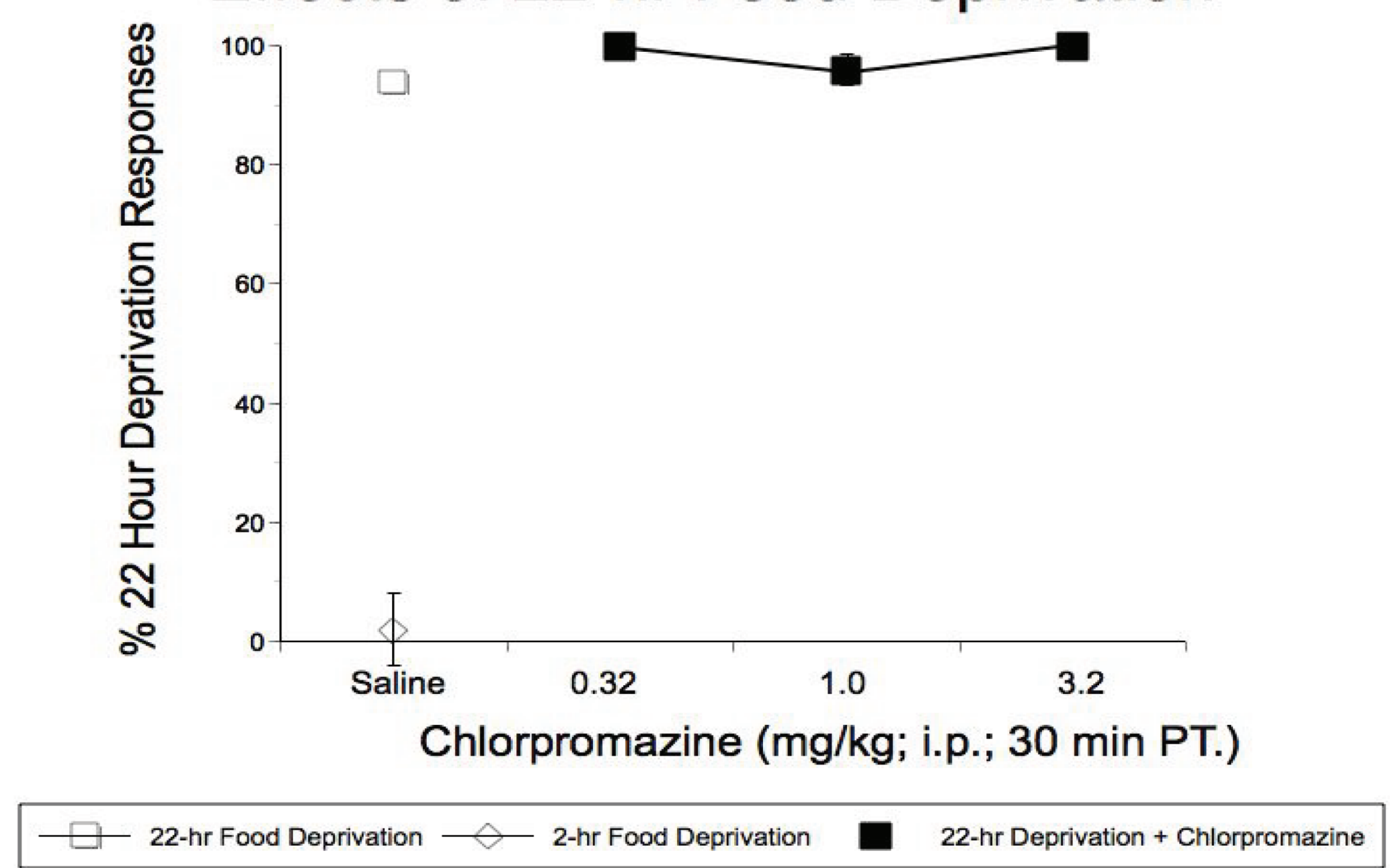
Generalized tests

Tests were conducted similar to two-cycle training sessions except for the following differences:

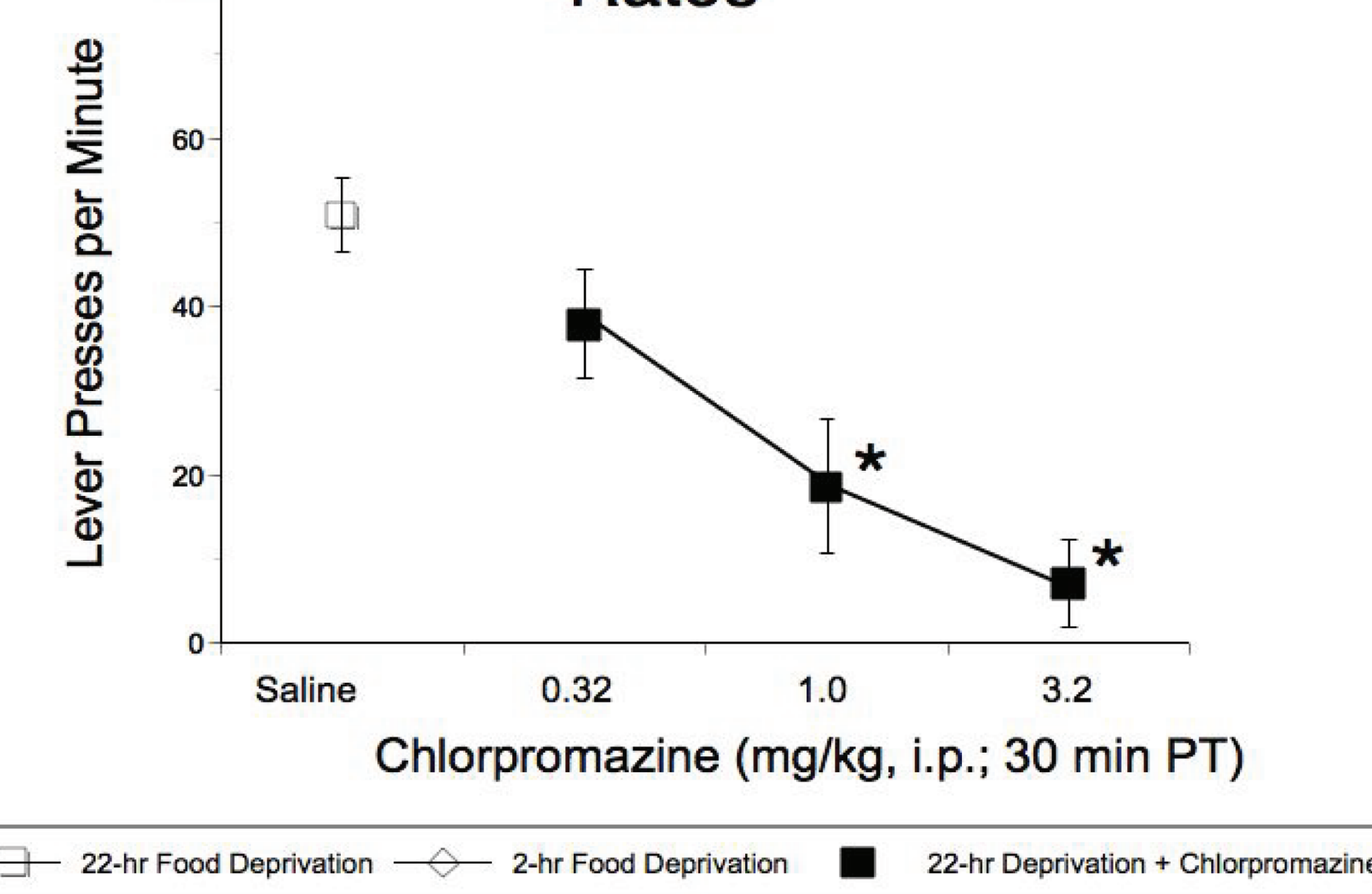
- Injections occurred 30 min before a test session
- Drug tests occurred only under the 22 hr deprivation condition, control tests occurred under both the 2 hr and 22 hr deprivation condition
- For test sessions, responses toward either lever were reinforced
- Following each test session subjects were placed in suspended cages with free access to food and water
- Food and water intake was measured after 1 hour
- Data were collected 30 and 60 min after the injection. Data obtained during the test 60 min after the injection that did not differ from those obtained 30 min post-injection are not shown
- Data were analyzed by ANOVA. If the results of the ANOVA were significant, Tukey post-hoc tests were implemented

Figures

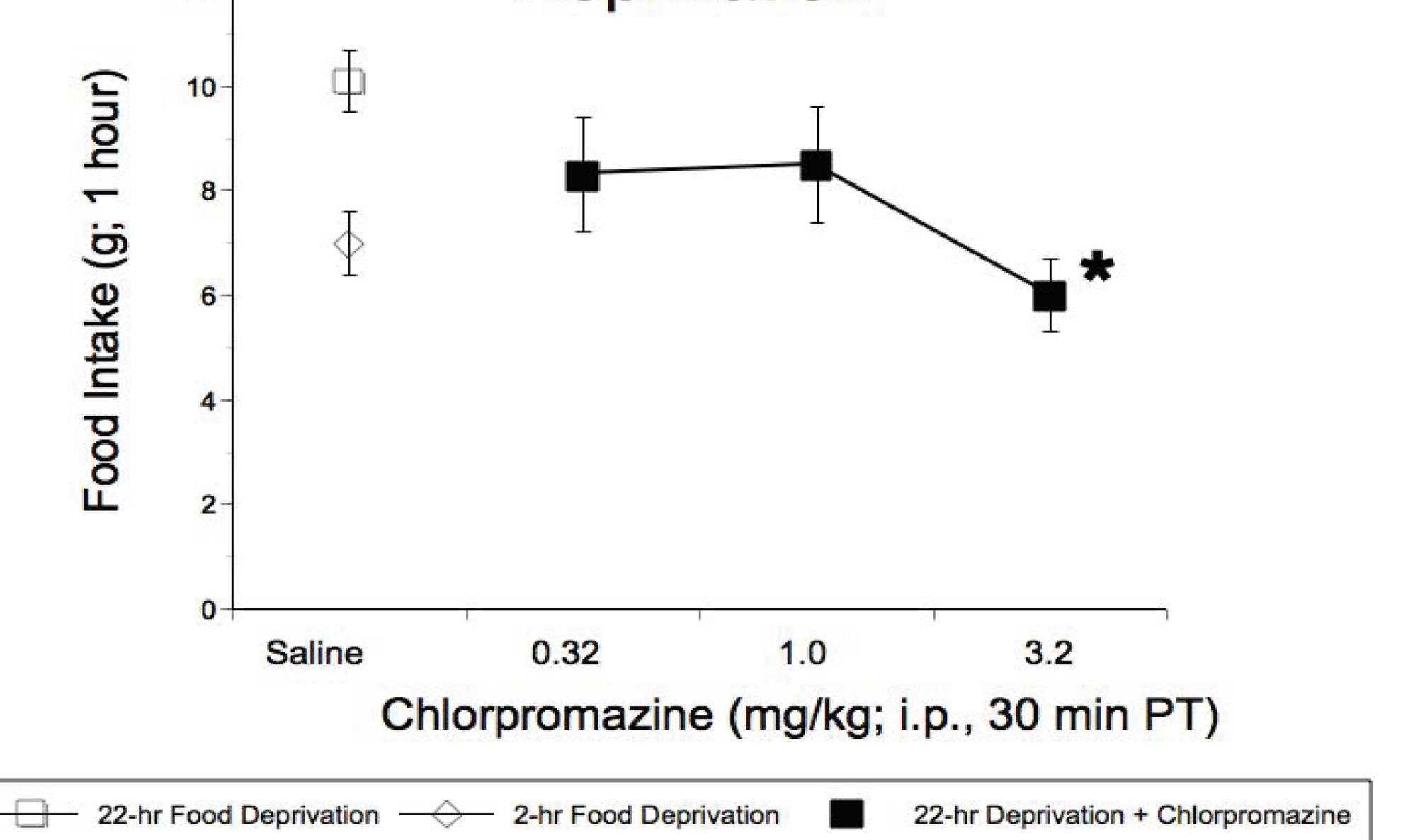
Chlorpromazine Does Not Alter the Stimulus Effects of 22-hr Food Deprivation



Chlorpromazine Decreases Response Rates



Chlorpromazine Decreases Consumption of Rodent Chow Following 22 Hour Food Deprivation



Results and Conclusions

- Chlorpromazine did not alter the discriminative stimulus effects of 22 hr food deprivation.
- Chlorpromazine (1.0mg/kg and 3.2mg/kg) significantly decreased response rates.
- Chlorpromazine (3.2mg/kg) significantly decreased food intake following 22 hr food deprivation.

Chlorpromazine did not alter the discriminative stimulus effects of 22 hr food deprivation, but did significantly decrease response rates and food intake. These results suggest chlorpromazine alters food consumption by mechanisms not related to internal states associated with acute food deprivation. Similar to previous research, response rate was dose-dependently decreased in our study. Food intake was significantly decreased only at the largest dose (3.2mg/kg). This supports other experimental results which have found that larger doses (5.0mg/kg-10mg/kg) of chlorpromazine may initially suppress eating. These studies have also found that chlorpromazine may actually begin to increase food intake after a longer period of time (beyond 2 hours). This suggests that chlorpromazine may affect food intake in two time phases. In order to evaluate chlorpromazine's possible two phase mechanism in our paradigm, we will measure the drug's ability to alter the discriminative stimulus effects of 22 hr food deprivation at larger doses. We will also evaluate the effects of chlorpromazine on food intake over a longer time course (4 hours post-injection).

Previous Results

Chemicals that increase eating and induce effects similar to 22 hour food deprivation	ghrelin, neuropeptide Y
Chemicals that increase eating and do not induce effects similar to 22 hour food deprivation	butorphanol, DAMGO, orphanin FQ, pentobarbital
Chemicals that decrease eating and reduce the effects of 22 hour food deprivation	cholecystokinin, sibutramine
Chemicals that decrease eating and do not reduce the effects of 22 hour food deprivation	exendin-4, naltrexone, oxytocin, rimonabant

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