

# Effects of duloxetine in rats trained to discriminate between 2- and 22-hr food deprivation



M.A. Vanden Avond, A.R. Johnson, K.A. Reed, B.R. Gomer, D.J. Nemece, E.J. Hendrickson, A.T. Schultz, C.A. Toddles, T.J. Vossen, M.M. Dregler, B.M. Berti, D.C. Jewett

## Introduction

Duloxetine inhibits serotonin and norepinephrine transporters, and is clinically used to treat depression, pain, and generalized anxiety disorder. Duloxetine has been shown to reduce food intake in several species. Sibutramine, a drug that also inhibits serotonin and norepinephrine transporters, was clinically used to treat obesity before being recalled by the FDA. Previous studies have shown that sibutramine disrupts the discriminative stimulus associated with 22-hr food deprivation (Jewett et al., 2009). Chudasama and Bhatt (2009) measured body mass index and food intake and examined the effects of duloxetine and sibutramine in obese rats. Though sibutramine and duloxetine have both been shown to decrease food intake in obese rats, duloxetine significantly decreased food intake in the first and second weeks of administration when compared to sibutramine. In the present investigation, we examined the effects of duloxetine in non-restricted rats trained to discriminate between 22- and 2-hr food deprivation to gain better understanding of neurochemicals mediating the discriminative stimulus effects of 22-hr food deprivation.

## Method

### Subjects and Apparatus

- Male Sprague-Dawley rats were housed in individual cages in a room with 12:12 light/dark cycle.
- 45-mg food pellets (BioServe F#0021) were delivered as reinforcers in standard two-lever operant chambers (Med-Associates).

### Drug

- Duloxetine (3.2-17.8 mg/kg) was dissolved in 0.9% saline and administered s.c.

### Behavioral Training

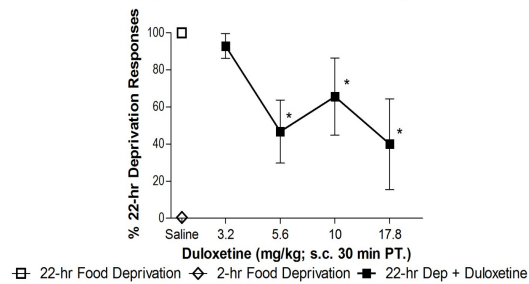
- Condition appropriate lever presses (left lever presses following 22-hr food deprivation, and right lever presses following 2-hr deprivation) were reinforced under a FR-15 reinforcement schedule.
- Training continued until subjects emitted greater than 80% condition-appropriate responses both prior to the first reinforcer delivery for each training cycle and for the complete training session.

### Generalization Tests

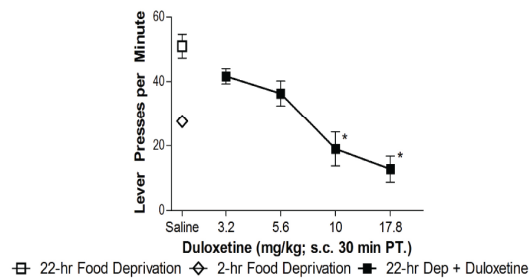
- A cumulative dosing procedure was implemented during test sessions.
- Responses toward either lever were reinforced under a FR-15 reinforcement schedule.
- Saline (s.c.) was administered prior to the response period.
- Duloxetine (3.2 to 17.8 mg/kg, 30 min PT) was administered prior to subsequent response periods.
- Following the last response period for a session, subjects were placed in suspended cages with free access to food and water for one hour.

## Figures

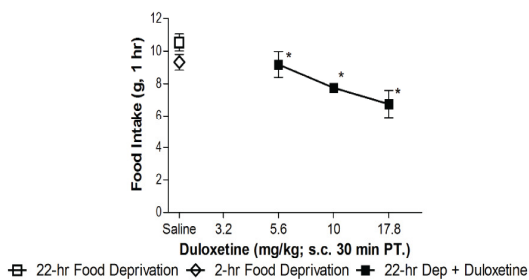
Effects of Duloxetine on the Discriminative Stimulus Effects of 22-hr Food Deprivation



Effects of Duloxetine on Response Rate



Effects of Duloxetine on Food Intake



## Results and Conclusion

- Administration of duloxetine (5.6 -17.8 mg/kg, s.c.) significantly decreased the discriminative stimulus effects of 22-hr food deprivation.

- Duloxetine (10 -17.8 mg/kg, s.c.) also resulted in significantly decreased rates of lever pressing

- Duloxetine (5.6 - 17.8 mg/kg, s.c.) reduced food intake induced by 22-hr food deprivation.

These findings are consistent with our laboratory's previous findings with sibutramine, and offer further evidence that serotonin and norepinephrine are important in regulating internal states associated with food consumption. Further investigation is necessary to determine the mechanisms through which these two neurochemicals interact with neural systems in order to regulate physiological and behavioral aspects of food consumption. Understanding these processes may provide important insight into an array of abnormal regulation of food intake such as obesity.

## Previous Results

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

## Acknowledgements

- University of Wisconsin - Eau Claire Office of Research and Sponsored Programs
- University of Wisconsin - Eau Claire Faculty/Student Research Collaboration
- University of Wisconsin - Eau Claire Differential Tuition Program
- University of Wisconsin - Eau Claire Student Travel for the Presentation of Research Results