Lisdexamfetamine-induced suppression of binge-eating in rats is attenuated by the α2-adrenoceptor antagonist, prazosin
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ABSTRACT
Background: Binge-eating disorder (BED) is a common psychiatric condition, affecting ~2% of the adult population and presents as the frequent, compulsive, excessive consumption of highly palatable foods. We have recently developed and pharmaco-chemically characterized a rat model of BED in which rats are given irregular, limited access to chocolate intake following a brief period of ad libitum access to normal food and water, allowing for the novel pruning of an eating disorder that is currently used for the treatment of attention-deficit/hyperactivity disorder in children aged 6-18 years and adults. We have previously shown that lisdexamfetamine in a rat model of binge eating did not reduce consumption of chocolate at low doses. The present study was conducted to determine if lisdexamfetamine reduced consumption of chocolate at the lowest doses that produced reductions in chow intake.

Methods: Female rats maintained on a reverse dark-light cycle were given free access to normal food and water, and in addition were allowed brief (2h), irregular access to chocolate during the dark phase over a period of 4 weeks. During this period, rats given intermittent access to chocolate developed robust binge-eating behavior that consisted of profound hyperphagia of chocolate and reductions of normal food intake on the days immediately following the binge session. Preliminary experiments to select doses for subsequent studies investigated the effects on chocolate and normal food consumption of doses of LDX (0.1-1.5 mg/kg po) and doses of the antagonists: prazosin (0.01-10 mg/kg ip), prazosin (0.01-0.5 mg/kg ip), SCH23390 (0.01-3 mg/kg ip), SCH23390 (0.01-0.3 mg/kg ip), raclopride (0.05-3 mg/kg ip) and raclopride (0.05-0.1 mg/kg ip). In the present study, we administered lisdexamfetamine in the contrasted doses before a 2h binge session, conducted in the rats which were selected for the previous dose selection experiment.

Results: LDX did not reduce the binge consumption of chocolate in the 2h binge session (vehicle = 197 ± 7; LDX-0.005 mg/kg po = 166 ± 16; NS to LDX-0.1 mg/kg po = 07 ± 0.7, p<0.001 and p<0.5, respectively). Administration of lisdexamfetamine did not reduce consumption of chocolate relative to normals in the binge session. There was a significant effect of antagonist in the interaction of the study. The effect of LDX on chocolate bingeing was partially reversed in a dose-related manner by prazosin and SCH23390 (0.3 mg/kg ip), suggesting that the effect of LDX is not mediated by dopaminergic release acting through D1 or D2 receptors.

CONCLUSIONS
• The dose-dependence for this attenuation appears to be relatively low, and may represent a ceiling effect.
• The dose-dependence for this attenuation appears to be relatively low, and may represent a ceiling effect. We will also assess the extent to which the attenuation is mediated through α2 and α2-adrenoceptors.

INTRODUCTION
Binge-eating disorder (BED) is a psychiatric condition affecting ~2% of the US adult population. Binge-eating disorder is manifest as the compulsive, excessive consumption of highly palatable foods. Binge-eaters frequently experience intense feelings of guilt and anxiety after a binge session, but do not indulge in purging. BED is often associated with obesity, but a significant proportion of sufferers are normal weight. Lisdexamfetamine mesylate (LDX) is a novel produg that is metabolized to d-amphetamine primarily by red blood cells. LDX is approved to treat ADHD in children (6-12 years) and adults.

Methods
Female lean rats maintained on a reverse dark-light cycle were given free access to normal food and water, and in addition were allowed brief (2h), irregular access to chocolate during the dark phase over a period of 4 weeks. During this period, rats given intermittent access to chocolate developed robust binge-eating behavior that consisted of profound hyperphagia of chocolate and reductions of normal food intake on the days immediately following the binge sessions. The bodyweights of the binge eating rats were not significantly different from the controls.

Preliminary experiments to select doses for subsequent studies investigated the effects on chocolate and normal food consumption of doses of LDX (0.1-1.5 mg/kg po) and doses of the antagonists: prazosin (0.01-10 mg/kg ip), prazosin (0.01-0.5 mg/kg ip), SCH23390 (0.01-3 mg/kg ip), SCH23390 (0.01-0.3 mg/kg ip), raclopride (0.05-3 mg/kg ip) and raclopride (0.05-0.1 mg/kg ip).

RESULTS
• Figure 1 shows that lean, female Wistar rats given intermittent, limited access to chocolate developed robust patterns of binge-eating behavior.
• LDX dose-dependently reduced the rats’ consumption of chocolate in the 2h binge session (Figure 2A). In this experiment, LDX had no effect on the consumption of normal food (Figure 2B).
• The doses of prazosin, SCH23390, raclopride or SCH23390 used in the antagonist experiments did not alter the consumption of chocolate or total food intake in the 2h binge session (Table 1).
• As shown in Figure 3A, chocolate consumption was decreased by ~90% by LDX (1.0 mg/kg po) and this reduction was partially reversed in a dose-related manner by prazosin.
• Chocolate bingeing reduced by LDX was not significantly modified by RX218012 (Figure 3A), SCH23390 or raclopride (Figure 4A and B).