GABA Neurotransmission in an Animal Model of Binge Eating Disorder: Effects of Lisdexamfetamine

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Abstract

Background: Binge eating disorder (BED) is a psychiatric impulse control disorder that is characterized by compulsive overeating episodes. The main symptoms of the disorder include frequent binge-eating episodes that are accompanied by feelings of extreme anxiety and helplessness during or after binging. We developed an animal model of binge eating in which adult, female rats were given unpredictable, limited access to chocolate (Vickers et al., 2015). These binge-eating rats showed compulsive consumption when given access to palatable food (Heal et al., 2016) and increased cognitive impulsivity in a chocolate rewarded delay discounting task (Vickers et al., 2017), suggesting that the model also mimics some of the underlying psychopathology of BED. Furthermore, all of these dysregulated behaviors were prevented by administration of lisdexamfetamine (LDX). We evaluated expression of two GABAAergic biomarkers (GAD65 mRNA and GAD67 mRNA) using in situ hybridization in binge-eating animals, and then examined the effects of LDX, which was recently approved for treatment of BED, on the same GABA biomarkers.

Methods: We collected forebrain tissue from 4 groups of rats (N=8/group):

Cohort 1, Group A: rats were given access to chocolate (24 hr) + empty pot (2 hr on an irregular access schedule), as described by Vickers et al. (2015). Rats in Cohort 1 represent the control groups.

Cohort 1, Group B: non-binge control rats were treated with LDX (0.8 mg/kg).

Cohort 2, Group A: rats were given access to chocolate (24 hr) + a junk food (powdered chocolate) for bingeing 2 hr on an irregular access schedule. Animals in Cohort 2 represent a model of BED.

Cohort 2, Group B: binge-eating rats were treated with LDX (0.8 mg/kg).

On Day 30, rats allocated to drug treatment were given LDX (0.8 mg/kg) po 1 hr prior to a final 2 hr bingeing session on chocolate or presentation of empty pots to the control groups. Rats were killed and brains were taken 1 hr after the final test session. In situ hybridization was performed using two 48-base-long sequences from the rat mRNA sequence for GAD65 and GAD67. Two 49-base-long sequences from the rat mRNA sequence for GAD67 were labeled by 3'-tailling of Probes (5 pmol) were labeled by 3'-tailling of C-standards were exposed to Biomax-MR film for 5–7 days at 4°C in light-tight cassettes, developed, and fixed.

Conclusions: These results provide the first evidence that the expression of GABA biomarkers (GAD65 and GAD67 mRNA) is reduced in an animal model of BED compared to control animals. These findings suggest that alterations in GABA neurotransmission in the frontal cortex and nucleus accumumbens may contribute to the impulsive behaviors observed in BED patients. LDX-induced normalization of GAD65 and GAD67 mRNAs in the binge-eating rats reversed the observed reduction in GAD65, GAD67 mRNA expression in MPC (by 10%), DFC (by 10%), NaC-C (by 17%) and NaC-S (by 16%) (all P<0.05). The expression of GAD65 and GAD67 mRNA expression was significantly reduced in MPC, DFC, NaC-C, NaC-S, CP-M, and CP-L (all P<0.05). There were no changes in GAD65 and GAD67 mRNAs in any of the assessed forebrain regions. This study replicated previous findings of reduced forebrain GABA biomarkers (GAD65 and GAD67 mRNA expression) in an animal model of BED. This study also extends previous observations by demonstrating that LDX reverses GAD65 and GAD67 mRNA expression reductions in the frontal cortex and NAc of binge-eating rats but not in control vehicle-treated rats. Taken together, these data support the hypothesis that alterations in GABA neurotransmission in the frontal cortex and NAc may contribute to the impulsive behaviors observed in BED and that the effects of LDX may be partially mediated by restoration of GABA neurotransmission in the frontal cortex and NAc.

References


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Conflicts of Interest

David J. Heal serves on the board of directors for the National Institute on Drug Abuse (NIDA). He has received grants from NIDA and other foundations. He is a consultant for Shire, Inc., which manufactures the investigational drug LDX.

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