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Baclofen suppresses binge eating of pure fat but not a sugar-rich or sweet-fat diet

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Abstract

Baclofen is a gamma-aminobutyric-acid-B (GABA-B) agonist that is known to reduce the intake of some drugs of abuse. Binge eating of sugar or fat has been shown to have behavioral and neurochemical similarities to drug abuse, and may be special cases suggestive of natural addiction. In order to determine whether a treatment for drug abuse would have an effect on binge eating, and if so, which type of food intake might be affected, the present study compared the effects of baclofen on binge eating sucrose, fat, and a sweet-fat combination. Rats were maintained for 21 days on a schedule of 12-h daily access to (1) a 10% sucrose solution, (2) vegetable fat, or (3) a commercially available sweet-fat chow. A fourth group had only 2-h daily access to vegetable fat. All four experimental groups, plus a control group, had free access to water and standard rodent chow. Food intake was then measured following i.p. administration of baclofen (0, 0.6, 1.0, or 1.8 mg/kg). Results showed that while there was no effect of drug on standard chow intake of rats in any group, baclofen stimulated binge eating of sweet-fat food, suppressed binge eating of pure fat (vegetable shortening) in the group with 2-h access, and had no effect on sucrose binges. These results support previous findings of a suppressive effect of baclofen on binge eating of fat and introduce a new finding that the drug differentially affects binge eating of sucrose and a sugar-fat combination.

Keywords

animal model; GABA; bulimia; binge eating disorder; rat

Baclofen is an agonist at GABA-B receptors that can reduce the rewarding effects of substances of abuse (Brebner et al. 1999, 2000, 2005; Ranaldi and Poeggel 2002; Di Ciano and Everitt 2003; BRoberts 2005). The effect of baclofen on food intake in normal rats is generally stimulatory (Higgs and Barber 2004; Patel and Ebenezer 2008). However, baclofen can decrease feeding in diet-induced obese or diabetic (db/db) mice (Sato et al. 2007). Baclofen also attenuates binges (Buda-Levin et al. 2005) and significantly reduces conditioned responding for fat (Wojnicki et al. 2006) in rats with a history of daily binge eating of vegetable fat. Clinical findings have also shown baclofen to be effective in reducing binge eating in patients with binge eating disorder or bulimia nervosa (Broft et al. 2007).

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Binge eating is defined as repeated, discrete, intermittent bouts of consuming unusually large amounts of food (American Psychiatric Association, 2000). While previous studies suggest that baclofen attenuates binge eating of fat, little is known of the drug's effects on the intake of other macronutrients. Foods consumed during binge episodes in a clinical population, though usually high in fat, are usually also high in sugar content (Hadigan et al. 1989; Guertin and Conger 1999). Therefore, in the present study, we investigated the ability of baclofen to attenuate binges on other palatable foods, specifically a sucrose solution and a sweet-fat combination.

Methods

Diet Groups and Injection Procedures

All experiments used male Sprague-Dawley rats obtained from Taconic Farms (Germantown, NY). Rats were housed individually on a 12-h reversed light: dark cycle. All rats had free access to water and standard chow (LabDiet #5001, PMI Nutrition International, Richmond, IN; 10% fat, 20% protein, 70% carbohydrate, 3.02 kcal/g). Rats (N=50) weighing 300-400 g at the onset of the experiment were divided into five groups matched for body weight.

The three groups with 12-h access received the palatable food 4 h after the onset of the dark cycle as follows: (1) The 12-h Sweet-fat group (n=10) received 12-h daily access to sweet-fat chow (Research Diets, New Brunswick, NJ, #12451; 45% fat, 20% protein, 35% carbohydrate, 4.7 kcal/g, nutritionally complete). (2) The 12-h Vegetable Fat group (n=10) received daily access to Crisco All-Vegetable Shortening (The J.M. Smucker Co., Orrville, OH; 9.17 kcal/g). (3) A 12-h Sucrose group (n=10) received a 10% sucrose solution (0.375 kcal/mL). This 12-h access schedule is a variant of that used in our prior publications (Colantuoni et al. 2001; Colantuoni, Rada et al. 2002; Avena et al. 2006). To replicate the findings of Corwin and colleagues (Buda-Levin, Wojnicki et al. 2005), this experiment also included a 2-h Vegetable Fat group (n=10) that received daily access to Crisco from 4 to 6 h after the onset of the dark cycle. The free-access Chow group (n=10) served as a control. Body weights and intakes of palatable food and chow were measured weekly. Due to the number of rats and the design of this experiment, not all of the groups were tested together.

After 21 days of palatable-food access, drug testing began. Using a counterbalanced, experimenter-blind design, (R)-baclofen (Tocris, Ellisville, MO) diluted in 0.9% saline was injected i.p. at doses of 0.6, 1.0, and 1.8 mg/kg. Each of these doses were assigned using a uniform Latin square and had been previously tested with paradigms including 2-h access to vegetable fat (Buda-Levin et al., 2005; Wojnicki et al., 2006). On the first day of testing for each dose, half of the rats received baclofen injections, and the other half received 0.9 % saline vehicle. Injections were reversed on the second day of testing. Doses were separated by 5-day intervals.

All food was removed for 30 min after injections were administered (30 min prior to the normal palatable-food access period), then the measurements with chow and the palatable diets began, 4 h after the onset of the dark cycle.

Statistical Analysis

All intake data were converted into calories. Repeated measures ANOVAs with *post-hoc* Bonferonni pair-wise comparisons were used to analyze intake and bodyweights prior to testing. Mixed-factorial ANOVAs were used to analyze, across all five groups, overall main effects and interactions of baclofen injection, dose, and group for 2-h palatable intake and standard chow intakes. Within each group, two-way ANOVAs were performed to analyze main effects and interactions of dose and drug. *Post-hoc* one-way ANOVAs were used to

analyze effects of dosage, and t-tests comparing baclofen to vehicle at each dose were used to analyze interactions of drug and dose effects. Cohen's *d* values, as a measure of effect size, were calculated for these vehicle-baclofen comparisons.

Results

Intake Behavior Prior to Testing

There was a significant main effect of group in terms of palatable intake ($F(3,36)=31.17$, $p<0.001$), with the rats in the 12-h Sweet-fat group consuming more calories of palatable food during their access period than any other group ($p<0.001$ compared to all other groups with access to palatable food); however, there were no statistically significant differences, across the 21 days of access, in total 24-h caloric intake among any groups, including the free-access chow group. Pre-injection intake data are presented in Table 1.

Over the 21-day access period prior to baclofen testing, bodyweights diverged between groups ($F(4,45)=3.64$, $p<0.01$). Further analysis showed that this effect of group was due to the higher bodyweights of rats in the 12-h Sucrose group, which came to be significantly higher than those of rats in the 2-h Vegetable Fat group over the 21 days ($p<0.02$). Despite differences in intake of palatable food among the experimental groups, caloric compensation in chow intake resulted in no other significant differences in body weight over the 21-day access period prior to baclofen testing.

Baclofen Attenuates Vegetable-fat Binge Eating, But Increases Sweet-fat Binge Eating with No Effect on Sucrose Binges or Standard Chow Intake

Overall, there was a significant dose x group x drug interaction (Figure 1; $F(8, 88)=3.40$, $p<0.002$). There was a significant effect of baclofen versus vehicle on the subsequent 2-h palatable chow intakes of rats in both the 12-h Sweet-fat group ($F(1, 9)=8.95$, $p<0.02$) and the 2-h Vegetable Fat group ($F(1, 9)=7.74$, $p<0.025$), with baclofen increasing intake in the 12-h Sweet-fat group, and decreasing intake in the 2-h Vegetable Fat group. There was also a significant dose x drug interaction in the palatable food intake of rats in the 2-h Vegetable Fat group ($F(2, 18)=5.90$, $p<0.02$). Post-hoc paired samples t-tests revealed that while all doses suppressed the group's mean 2 h intake of vegetable fat, the highest dose of baclofen (1.8 mg/kg, i.p.) significantly suppressed binge eating of vegetable fat ($t(9)=-4.21$, $p<0.002$, $d=-1.53$).

There was a significant main effect of dose ($F(2, 18)=5.10$, $p<0.02$) on the 2-h palatable food intake of rats in the 12-h Vegetable Fat group. However, *post-hoc* one-way ANOVA did not reveal a significant difference in intakes among doses ($p=0.085$), and the dose effect was likely due to the group's larger intake following the 0.6mg/kg dose. There was no effect of drug or dose on the intakes of rats in the 12-h Sucrose group or the free-access Chow group.

There was no significant main effect of drug or dose on standard chow intake in any of the five groups.

Discussion

Baclofen differentially affected binge eating behavior. Vegetable-fat binges were suppressed in rats with daily 2-h access, sweet-fat binges were enlarged, and sucrose-solution binges were not affected. This confirms the results of Corwin and colleagues (Buda-Levin et al. 2005), in that 1.8 mg/kg baclofen (i.p.) significantly suppressed binge eating in rats with 2 h daily access to vegetable fat. Others have reported that a much higher dose (5 mg/kg) can reduce responding for sucrose (Petty and Heyman 1997). The present results suggest that

baclofen has a suppressive effect on binge eating of fat and an interesting reverse effect on the intake of a sweet-fat combination.

In the present study, the observed effects of baclofen on binge eating of a sweet-fat mixture differed from the results of prior research: Wong and colleagues (2009) recently found that baclofen decreased intake of a 10% sucrose sweet-fat combination and had no effect on the intake of limitedly-available sweet-fat mixtures with higher sucrose concentrations (32%), while the present study found that baclofen augmented intake of a sweet-fat mixture that was high in sucrose (17%) and was provided on a limited access schedule. Prior research has found that baclofen, at high doses, can increase the intake of other nutritionally complete chows, like standard rodent chow (Ebenezer, 1995), and perhaps the sweet-fat intake increase we observed was due to the chow's nutritional completeness. Conversely, there was no effect of baclofen on the standard-chow intake of rats in the present study, which would suggest that the present findings of increased intake are binge-specific.

It is not known why baclofen, at doses that suppress fat intake, increases the size of sweet-fat combination binges. These differential effects seem to be consistent, however, with findings of differences in addictive-like behavior in rats that binge eat sugar vs. fat (Avena et al., 2009). It is possible that plain fat and sweetened fat engage different GABAergic systems and that something about the addition of sugar to high-fat food, perhaps increased palatability, overcomes the binge-suppressing effects of baclofen. Further, previous studies have found that baclofen, when administered i.p., has very different effects on self-administration of substances of abuse, binge eating, and normal eating behaviors, depending on time and dose. Baclofen (1.0 mg/kg) significantly reduced responding for alcohol, but not sucrose, and a dose of 3.0 mg/kg significantly reduced responding for both (Janak and Michael Gill 2003). However, in another study, baclofen, administered at similarly high doses (2.0 and 4.0 mg/kg), increased responding for a highly-palatable mixture of sucrose, milk, and malted food powder (Ebenezer 1995).

Although the present experiment tested a systemic dose of baclofen, its effects on binge eating are presumed to be the result of agonist actions on GABAergic systems in the brain. Previous studies with drugs of abuse support this hypothesis. When injected either i.p. or locally in the nucleus accumbens or ventral tegmental area (VTA), baclofen can reduce cocaine self-administration in rats (Shoaib et al. 1998). When injected into the VTA, baclofen also reduces the reinforcing effects of heroin (Xi and Stein 1999), although this effect is not seen when baclofen is given i.p. (Di Ciano and Everitt 2003).

The contrasting effects of baclofen on binge eating of fat vs. a sugar-fat combination may also be attributed to neurological changes downstream of GABA. For example, studies suggest that the neuropeptide galanin stimulates fat intake, while neuropeptide Y (NPY) stimulates carbohydrate intake (Wang et al. 1998), and galanin seems to have an inhibitory action on NPY in the hypothalamus (Parrado et al. 2007). A high-carbohydrate diet increases NPY expression, and a high-fat diet increases galanin expression (Leibowitz et al. 2004) while reducing NPY expression (Wang et al. 1998). Perhaps, then, if GABA agonism could inhibit galanin, and thus reduce pure fat intake in rats with a history of binge eating of fat, in the case of a combination of carbohydrate and fat, agonism of GABA by baclofen would block the antagonistic effects of galanin on NPY, thereby promoting intake.

Differences in food texture, levels of palatability, and baseline consumption may also have a role in the observed differential effects of baclofen on binge eating. Both oral and post-oral factors contribute to food preference (Sclafani, 2004), and each palatable diet in the present study differed in texture and may have differed in sweetness intensity. Because baclofen was peripherally injected, its effects on the different diets may have resulted from a modification

at the oral level, e.g. in a palatability or texture-specific way. However, in light of findings that baclofen decreases water intake but augments intake of a malted milk powder solution (Ebenezer, 1995), it is less likely that the effect of baclofen on liquid sucrose solution consumption is related to texture.

In summary, the effects of baclofen on binge eating may be macronutrient specific. The present study replicates previous findings that baclofen suppresses binge eating of pure fat in rats with a history of 2-h fat binges (Buda-Levin et al. 2005), but also finds that the drug can increase the size of sweet-fat binges and has no effect on pure-sugar binges or standard chow intake. These results support the hypothesis that GABA-B receptors are involved in inhibiting binge eating of fat and stimulating binge eating of sugar-fat combinations. The findings may inform future clinical studies of baclofen with patients with bulimia nervosa and binge eating disorder to discern whether the drug attenuates binges dominated by fats as opposed to those dominated by sugars.

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Figure 1. Effect of baclofen on 2-h caloric intake (mean ± SEM). Baclofen significantly affected the intake of rats in the 2-h Vegetable Fat group (* $p < 0.025$, A) by decreasing intake at the 1.8 mg/kg dose, compared to vehicle (** $p < 0.002$, A). The drug increased intake in the 12-h Sweet-fat group (* $p < 0.025$, B).

Table 1

Pre-Testing Caloric Intake (mean $\pm$ SD).

Group	Day 1			Day 7			Day 14			Day 21		
	Mean Intake (kcal)	% Palatable Food		Mean Intake (kcal)	% Palatable Food		Mean Intake (kcal)	% Palatable Food		Mean Intake (kcal)	% Palatable Food	
12-h Sweet-fat	93.54 $\pm$ 29.98	75%		100.07 $\pm$ 21.96	86%		84.60 $\pm$ 23.28	86%		85.17 $\pm$ 18.88	89%	
12-h Vegetable Fat	90.72 $\pm$ 38.41	26%		86.15 $\pm$ 7.96	35%		87.06 $\pm$ 9.91	28%		109.93 $\pm$ 9.82	44%	
2-h Vegetable Fat	88.53 $\pm$ 23.27	6%		80.28 $\pm$ 12.70	20%		90.70 $\pm$ 9.69	42%		80.11 $\pm$ 9.28	41%	
12-h Sucrose	118.41 $\pm$ 23.90	12%		101.41 $\pm$ 12.27	26%		93.53 $\pm$ 14.05	24%		98.01 $\pm$ 12.68	27%	
<i>Ad Libitum</i> Chow	95.13 $\pm$ 14.07	n/a		84.71 $\pm$ 8.51	n/a		85.89 $\pm$ 8.34	n/a		89.30 $\pm$ 14.65	n/a	