

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

Laura A. Berner^a, Miriam E. Bocarsly^a, Bartley G. Hoebel^a and Nicole M. Avena^{a,b}

Baclofen is a γ -aminobutyric acid-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. 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, this 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 (i) a 10% sucrose solution, (ii) vegetable fat, or (iii) 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 *ad libitum* access to water and standard rodent chow. Food intake was then measured after intraperitoneal administration of baclofen (0, 0.6, 1.0, or 1.8 mg/kg). Results showed that although 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 earlier 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. *Behavioural Pharmacology* 20:631–634 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Behavioural Pharmacology 2009, 20:631–634

Keywords: animal model, binge eating disorder, bulimia, gamma-aminobutyric acid, rat

^aDepartment of Psychology, Princeton University, Princeton, New Jersey and ^bLaboratory of Behavioral Neurobiology, The Rockefeller University, New York, USA

Correspondence to Dr Nicole M. Avena, PhD, The Rockefeller University, 1230 York Avenue, Box 278, New York, NY 10021, USA
E-mail: navena@rockefeller.edu

Received 17 April 2009 Accepted as revised 10 August 2009

Introduction

Baclofen is an agonist at γ -aminobutyric acid-B (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; Roberts, 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).

Binge eating is defined as repeated, discrete, intermittent bouts of consuming unusually large amounts of food (American Psychiatric Association, 2000). Although earlier 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 also usually high in sugar content (Hadigan *et al.*, 1989; Guertin and Conger, 1999). Therefore, in this 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, New York, USA). Rats were housed individually on a 12-h reversed light/dark cycle. All rats had *ad libitum* access to water and standard chow (LabDiet #5001, PMI Nutrition International, Richmond, Indiana, USA; 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 palatable food 4 h after the onset of the dark cycle as follows: (i) the 12-h Sweet-fat group ($n = 10$) received 12-h daily access to sweet-fat chow (Research Diets, New Brunswick, New Jersey, USA, #12451; 45% fat, 20% protein, 35% carbohydrate, 4.7 kcal/g, nutritionally complete). (ii) The 12-h Vegetable Fat group ($n = 10$) received daily access to Crisco All-Vegetable Shortening (The J.M. Smucker Co., Orrville, Ohio, USA; 9.17 kcal/g). (iii) 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, 2002; Avena *et al.*, 2006). To replicate the findings of Corwin and colleagues (Buda-Levin *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 *Ad Libitum* Chow group ($n = 10$) served as a control. Body weights and intakes of palatable food and chow were measured weekly. Owing 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, Missouri, USA) diluted in 0.9% saline was injected intraperitoneally (i.p.) at doses of 0.6, 1.0, and 1.8 mg/kg. Each of these doses was assigned using a uniform Latin square and had been tested earlier 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.

Rats had access to only water for 30 min after injections were administered (30 min before the normal palatable-food access period), then the measurements of 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 analyses of variance (ANOVAs) with post-hoc Bonferroni pair-wise comparisons were used to analyze intake and body weights before 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 food 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 with 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 before testing

There was a significant main effect of group in terms of palatable food 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 with 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 *Ad Libitum* Chow group. Preinjection intake data are presented in Table 1.

Over the 21-day access period before baclofen testing, body weights diverged between groups [$F(4,45) = 3.64$, $P < 0.01$]. Further analysis showed that this effect of group was because of the higher body weights 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 before 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 \times group \times drug interaction [Fig. 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 \times 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 sample *t*-tests showed that although 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 [$t(9) = -4.21$, $P < 0.002$, $d = 1.53$].

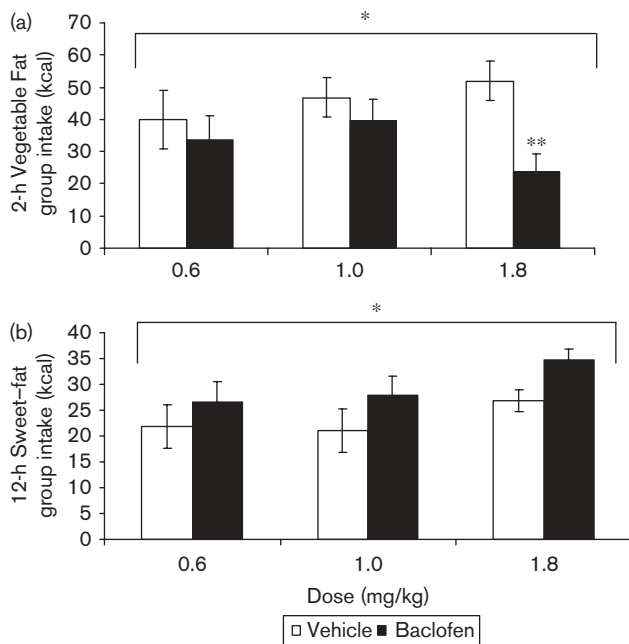
There was a significant main effect of dose [$F(2,18) = 5.10$, $P < 0.02$] on the 2-h palatable food intake of rats in the 12-h Vegetable Fat group. However, post-hoc one-way

Table 1 Pretesting 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	NA	84.71 \pm 8.51	NA	85.89 \pm 8.34	NA	89.30 \pm 14.65	NA

NA, not applicable.

Fig. 1



Effect of baclofen on 2-h caloric intake (mean \pm SEM). (a) Baclofen significantly affected the intake of rats in the 2-h Vegetable Fat group ($*P < 0.025$) by decreasing intake at the 1.8 mg/kg dose, compared with vehicle ($**P < 0.002$). (b) The drug increased intake in the 12-h Sweet-fat group ($*P < 0.025$).

ANOVA did not show a significant difference in intakes among doses ($P = 0.085$), and the dose effect was likely because of the group's larger intake after the 0.6 mg/kg dose. There was no effect of drug or dose on the intakes of rats in the 12-h Sucrose group or the *Ad Libitum* 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 (Petry 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 this study, the observed effects of baclofen on binge eating of a sweet-fat mixture differed from the results of prior research; Wong *et al.* (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%), whereas this 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, such as standard rodent chow (Ebenezer, 1995), and perhaps the sweet-fat intake increase we observed was because of the nutritional completeness of the chow. In contrast, there was no effect of baclofen on the standard-chow intake of rats in this 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 versus 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, earlier 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. Earlier studies with drugs of abuse support this hypothesis. When injected either i.p. or locally in the nucleus accumbens or ventral tegmental area, baclofen can reduce cocaine self-administration in rats (Shoaib *et al.*, 1998). When injected into the ventral tegmental area, baclofen also reduces the reinforcing effects of heroin (Xi and Stein, 1999), although this effect is not observed when baclofen is given i.p. (Di Ciano and Everitt, 2003).

The contrasting effects of baclofen on binge eating of fat versus 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, whereas 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 the 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 postoral factors contribute to food preference (Sclafani, 2004), and each palatable diet in this study differed in texture and may have differed in sweetness intensity. As baclofen was peripherally injected, its effects on the different diets may have resulted from a modification at the oral level, for example, 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. This study replicates earlier 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 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.

Acknowledgement

This research was supported by the USPHS grant AA-12882 (BGH) and DK-079793 (NMA).

References

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders, 4th edition, text revision*. Washington, DC: American Psychiatric Association.

Avena NM, Rada P, Hoebel BG (2006). Unit 9.23C sugar bingeing in rats. In: Crawley J, Gerfen C, Rogawski M, Sibley D, Skolnick P, Wray S, editors. *Current protocols in neuroscience*. Indianapolis: John Wiley & Sons Inc. pp. 9.23C.1–9.23C.6.

Avena NM, Rada P, Hoebel BG (2009). Sugar and fat bingeing have notable differences in addictive-like behavior. *J Nutr* **139**:623–628.

Brebner K, Froestl W, Andrews M, Phelan R, Roberts DC (1999). The GABA(B) agonist CGP 44532 decreases cocaine self-administration in rats:

demonstration using a progressive ratio and a discrete trials procedure. *Neuropharmacology* **38**:1797–1804.

Brebner K, Phelan R, Roberts DC (2000). Effect of baclofen on cocaine self-administration in rats reinforced under fixed-ratio 1 and progressive-ratio schedules. *Psychopharmacology (Berl)* **148**:314–321.

Brebner K, Ahn S, Phillips AG (2005). Attenuation of d-amphetamine self-administration by baclofen in the rat: behavioral and neurochemical correlates. *Psychopharmacology (Berl)* **177**:409–417.

Broft AI, Spanos A, Corwin RL, Mayer L, Steinglass J, Devlin MJ, *et al.* (2007). Baclofen for binge eating: an open-label trial. *Int J Eat Disord* **40**:687–691.

Buda-Levin A, Wojnicki FH, Corwin RL (2005). Baclofen reduces fat intake under binge-type conditions. *Physiol Behav* **86**:176–184.

Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, *et al.* (2001). Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport* **12**:3549–3552.

Colantuoni C, Rada P, McCarthy J, Patton C, Avena NM, Chadeayne A, *et al.* (2002). Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes Res* **10**:478–488.

Di Ciano P, Everitt BJ (2003). The GABA(B) receptor agonist baclofen attenuates cocaine- and heroin-seeking behavior by rats. *Neuropsychopharmacology* **28**:510–518.

Ebenezer IS (1995). Intraperitoneal administration of baclofen increases consumption of both solid and liquid diets in rats. *Eur J Pharmacol* **273**:183–185.

Guertin TL, Conger AJ (1999). Mood and forbidden foods' influence on perceptions of binge eating. *Addict Behav* **24**:175–193.

Hadigan CM, Kissileff HR, Walsh BT (1989). Patterns of food selection during meals in women with bulimia. *Am J Clin Nutr* **50**:759–766.

Higgs S, Barber DJ (2004). Effects of baclofen on feeding behaviour examined in the runway. *Prog Neuropsychopharmacol Biol Psychiatry* **28**:405–408.

Janak PH, Michael Gill T (2003). Comparison of the effects of allopregnanolone with direct GABAergic agonists on ethanol self-administration with and without concurrently available sucrose. *Alcohol* **30**:1–7.

Leibowitz SF, Dourmashkin JT, Chang GQ, Hill JO, Gayles EC, Fried SK, *et al.* (2004). Acute high-fat diet paradigms link galanin to triglycerides and their transport and metabolism in muscle. *Brain Res* **1008**:168–178.

Parrado C, Diaz-Cabiale Z, Garcia-Coronel M, Agnati LF, Covenas R, Fuxe K, *et al.* (2007). Region specific galanin receptor/neuropeptide Y Y1 receptor interactions in the tel- and diencephalon of the rat. Relevance for food consumption. *Neuropharmacology* **52**:684–692.

Patel SM, Ebenezer IS (2008). The effects of chronic intraperitoneal administration of the GABA B receptor agonist baclofen on food intake in rats. *Eur J Pharmacol* **593**:68–72.

Petry NM, Heyman GM (1997). Bidirectional modulation of sweet and bitter taste by chlordiazepoxide and Ro 15-4513: lack of effect with GABA drugs. *Physiol Behav* **61**:119–126.

Ranaldi R, Poeggel K (2002). Baclofen decreases methamphetamine self-administration in rats. *Neuroreport* **13**:1107–1110.

Roberts DC (2005). Preclinical evidence for GABAB agonists as a pharmacotherapy for cocaine addiction. *Physiol Behav* **86**:18–20.

Sato I, Arima H, Ozaki N, Ozaki N, Watanabe M, Goto M, *et al.* (2007). Peripherally administered baclofen reduced food intake and body weight in db/db as well as diet-induced obese mice. *FEBS Lett* **581**:4857–4864.

Sclafani A (2004). Oral and postoral determinants of food reward. *Physiol Behav* **81**:773–779.

Shoaib M, Swanner LS, Beyer CE, Goldberg SR, Schindler CW (1998). The GABA-B agonist baclofen modifies cocaine self-administration in rats. *Behav Pharmacol* **9**:195–206.

Wang J, Akabayashi A, Dourmashkin J, Yu HJ, Alexander JT, Chae HJ, *et al.* (1998). Neuropeptide Y in relation to carbohydrate intake, corticosterone and dietary obesity. *Brain Res* **802**:75–88.

Wojnicki FH, Roberts DC, Corwin RL (2006). Effects of baclofen on operant performance for food pellets and vegetable shortening after a history of binge-type behavior in non-food deprived rats. *Pharmacol Biochem Behav* **84**:197–206.

Wong KJ, Wojnicki FHW, Corwin RLW (2009). Baclofen, raclopride, and naltrexone differentially affect intake of fat/sucrose mixtures under limited access conditions. *Pharmacol Biochem Behav* **92**:528–536.

Xi ZX, Stein EA (1999). Baclofen inhibits heroin self-administration behavior and mesolimbic dopamine release. *J Pharmacol Exp Ther* **290**:1369–1374.