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Baclofen decreases feeding in non-human primates

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Abstract

This study examined how the $GABA_b$ agonist baclofen (0.5–5.6 mg/kg, p.o.), reported to increase food intake in rodents, affected the appetitive and consummatory aspects of feeding of non-human primates. Baboons had access to food 24 h each day, but they had to complete a two-phase operant procedure in order to eat. Responding on one lever during a 30-min appetitive phase was required before animals could start a consumption phase, where responding on another lever led to food delivery, i.e., a meal. Responding during the appetitive phase resulted in presentations of food-related stimuli only. Baclofen increased the latency to the first meal and decreased both appetitive and consummatory behavior. At the largest dose, baclofen induced emesis, indicating that the effects were due to malaise rather than a specific motivational action. In contrast, the positive control diazepam ($GABA_a$ agonist, 1.0–2.0 mg/kg, i.m.) decreased the latency to the first meal and increased both appetitive ($P<0.07$) and consummatory behavior. Although the baclofen-induced decrease in appetitive behavior replicates data obtained in rodents, the baclofen-induced decreases in consummatory behavior do not. The findings suggest that the effects of large doses of baclofen in non-human primates may, in part, be due to non-specific behavioral disruptions.

Keywords: Food intake; Baboon; Motivation; Baclofen; Diazepam

1. Introduction

Gamma-aminobutyric acid (GABA) is widely distributed in the central nervous system and functions as an inhibitory neurotransmitter (Krogsgaard-Larsen et al., 1987). GABA's modulatory role in endogenous dopamine release has been well-documented (Dewey et al., 1992). Striatal GABAergic neurons project, via the striatonigral and pallidonigral pathways, onto dopaminergic neurons within the pars compacta region of the substantia nigra, and exert a tonic level of inhibition on dopamine neurons (Kubota and McCulloch, 1983). The inhibition of pallidal GABAergic input to dopamine-containing neurons in the ventral tegmental area results in an increase in dopamine activity in the nucleus accumbens and olfactory tubercle. Clearly, dopaminergic and GABAergic systems are interrelated, and modulation of GABAergic transmission will affect dopamine transmission.

Because of the ability of GABAergic drugs to affect dopamine transmission, much recent experimental effort has been focussed on the potential utility of receptor subtype$_b$ ($GABA_b$) agonists as a pharmacological adjunct for the treatment of drug abuse (see review by Cousins et al., 2002). Baclofen (Lioresal®), a $GABA_b$ agonist, which relaxes skeletal muscle, is used clinically to treat muscle rigidity due to muscular dystrophy. The results across studies using laboratory rodents and a range of abused drugs are impressively consistent: $GABA_b$ agonists, including baclofen, are effective in reducing drug-taking behavior (Cousins et al., 2002). Of note is the general finding that reductions in drug taking in rodents occurred with minimal disruption of other consummatory behavior when multiple behaviors were recorded in the same study (see review by Roberts, 2005). In contrast to the data obtained with rodents, Weerts et al. (2005) reported that baclofen decreased both cocaine self-administration and food intake in baboons.

There is a large literature demonstrating that baclofen has significant effects on eating behavior. For example, several studies have shown that baclofen, at the dose range and routes used above, increases food intake in rats (Ebenezer, 1995; Ebenezer and Pringle, 1992; Stratford and Kelley, 1997; Ward et al., 2000), and at larger doses, decreases food intake in rats

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(Smith et al., 1999; Zarrindast et al., 1989). The effects of baclofen on food intake vary greatly across studies, however, with some studies reporting that baclofen, in the dose range reported to increase food intake, has no effect (e.g., Jonaidi et al., 2002), or decreases food intake (e.g., Addae et al., 1986).

In addition to possibly affecting food intake, baclofen has been shown to decrease the reinforcing efficacy of stimuli paired with primary reinforcement in rats (Colombo et al., 2003; Di Ciano and Everitt, 2003; Yun et al., 2004) and to decrease conditioned locomotor activity (Franklin and Druhan, 2000). Thus, baclofen may decrease appetitive behavior. But, baclofen increases rate of running in a runway for food, a measure of appetitive behavior in rats (Higgs and Barber, 2004), indicating that the behavioral effects of baclofen vary across studies and drug dose. Because of the variability in the data obtained in rodents and the paucity of data in non-human primates, the purpose of this study was to determine if baclofen would affect the appetitive and consummatory aspects of feeding using a laboratory model based on the procedures developed by Collier and colleagues (e.g., Collier et al., 1977; Collier, 1983).

In this procedure, baboons work for food by pulling on response levers, and food delivery is always accompanied by a visual signal, usually flashing lights. The food-related stimuli are conditioned reinforcers and baboons will work for the presentation of the stimuli only. Baboons have access to food 24 h each day, but they must complete a two-phase operant procedure in order to eat. Responding during the initial 30-min appetitive phase is reinforced by only the food-related stimuli, while responding during the latter consumption phase is reinforced with food and food-related stimuli. Every 10 responses completed during the appetitive phase are reinforced by the food-related stimuli (Kelleher, 1966). Completion of 10 responses on one lever starts the appetitive phase. Although the baboon needs to only make a minimum of another 10 responses, with the last response occurring after 30 min in order to switch to the consumption phase, baboons respond more often than the minimum amount. It is possible to see a wide range of responding during the appetitive phase (Berridge and Robinson, 1998). All of the responding during a single consumption phase comprises a single meal. While the appetitive phase must last about 30 min, the duration of the consumption phase is variable, as the phase continues until a baboon pauses eating for 10 min, i.e., meal duration and size can vary. In order to have another meal, the baboon must start another 30-min appetitive phase. Using variants of this procedure, we have reported that the anorectic drugs dexfenfluramine decreased both appetitive and consummatory behavior; and D-amphetamine increased appetitive, but decreased consummatory behavior (Foltin, 2001, 2004). The results replicate findings in laboratory rodents (Files et al., 1989; Fletcher, 1995, 1996; Kelley and Delfs, 1991; Robbins, 1978; Taylor and Robbins, 1984).

In addition to determining a complete dose–response function for baclofen we also tested, as a positive control, the $GABA_a$ agonist, diazepam. Using variants of this procedure, we have reported that diazepam increased both appetitive and consummatory behavior (Foltin, 2001, 2004), which replicates findings in laboratory rodents (Robbins et al., 1983). Finally, the effects of both drugs were determined in both male and female baboons.

2. Methods

2.1. Animals

Four male baboons (*Papio cynocephalus anubis*), weighing 9.1 to 12.7 kg, and four female baboons, weighing 8.1 to 10.8 kg, all of which were just entering puberty, were individually housed in standard non-human primate cages ($0.94 \times 1.21 \times 1.52$ m high) at The New York State Psychiatric Institute. The baboons had about 6 mo experience responding under FR schedules for food prior to the study. Body weights remained stable, or increased slightly over the study. The room was illuminated with fluorescent lighting from 7:00 AM to 7:00 PM daily. In addition to food earned during experimental sessions, two chewable vitamins, two pieces of fresh fruit, and a dog biscuit were also given daily. Water was available ad libitum from a spout located at the back of each cage. All aspects of animal maintenance and experimental procedures complied with the US National Institutes of Health Guide for Care and Use of Laboratory Animals, and were approved by the New York State Psychiatric Institute Animal Care and Use Committee.

2.2. Schedule of reinforcement

Responding under each phase of a two-phase chain schedule of reinforcement was on a separate response manipulandum [see Foltin (2001, 2004) for description of response panels]. The session began with the illumination of a single light above the appetitive lever. Completion of the first 10 responses on the appetitive lever began a 30-min timer and illuminated a second light over the appetitive lever, i.e., the 30-min appetitive phase was indicated by the illumination of two lights above the appetitive lever. The appetitive phase was a FI 30 min schedule, with a FR 10 second-order phase [FI 30′(FR 10:S)]. Thus, after every 10th response during the FI phase, the stimuli associated with reinforcer delivery during the second phase were presented. There was a 10 min limited hold for the appetitive phase, such that after the expiry of the 30 min FI, the next FR 10 had to be completed within 10 min. Failure to complete a FR 10 within 10 min canceled that appetitive phase, and extinguished one light over the appetitive lever such that only a single light was illuminated over the appetitive lever. The baboon received no indication that the 30-min interval had elapsed. The first FR 10 completed after 30 min resulted in the two lights above the left lever being extinguished and a single light above the right lever being illuminated, signalling the availability of food under the FR consumption phase of the chain schedule. The consumption phase of the chain schedule was maintained under a FR 10 schedule of food reinforcement (1 grain-based "dustless"® banana-flavored 1-g food pellet; 3.34 kcal/g: 20.1% protein, 3.3% fat, 55.3% carbohydrate,

3.3% ash, <5% moisture and 4.0% fiber; Bio-serv, Frenchtown, NJ). After a 10-min interval in which no responses occurred, the consumption phase terminated, i.e., meal size was determined by each baboon. The single light above the right consumption lever was then extinguished, and the single light above the left appetitive lever was again illuminated. In order to initiate another meal, the baboon was required to start another 30-min appetitive phase by pulling on the left lever.

Food pellets were accompanied by the illumination for 10 s of all 4 stimulus lights above both levers, and an additional 10 s of darkness, when all stimulus lights were extinguished. These stimuli were also presented after every 10th response during FI-appetitive phases. Daily sessions began each day, seven days a week, at 0900.

2.3. Procedure and drugs

Baclofen [(±)-b-(Aminomethyl)-4-chlorobenzenepropanoic acid; 0.50–5.6 mg/kg, Sigma Chemical Corp., St. Louis, MO] was given orally by placing baclofen powder in a fig on Tuesday and Friday of each week at 0900, with figs not containing baclofen given occasionally on other days of the week. A complete dose–response function was determined in 2 to 3 weeks in the following order: 1.0, 0.50, 3.2 and 5.6 mg/kg. Doses were administered only when responding on the two previous days was stable. The dose range was based on studies with rhesus monkeys (e.g., Negus et al., 2000; Tarika and Winger, 1980), but because no data were available in baboons, the doses were tested in ascending order as a safety precaution. The effects of diazepam (1.0–2.0 mg/kg, courtesy of Hoffman LaRoche, Nutley, NJ) were then assessed, also in ascending order, over a 2-wk period. Diazepam [35 mg/ml emulsified in a 1:1 ratio of polyethoxylated vegetable oil (Emulphor-620, GAF Co., New York, NY) and a 95% ethanol mixture] was given intramuscularly (i.m.) in a thigh muscle (location varying among sessions), with volumes ranging between 0.2 and 0.8 ml, on Tuesday and Friday of each week at 0900, with placebo injections given occasionally on other days of the week. Larger diazepam doses were not tested due to significant sedation following the 2.0 mg/kg dose. All baboons were tested with all doses of both drugs.

2.4. Data analysis

The total number of light presentations during appetitive phases and total number of food pellets (with light presentations), number of meals (consumption phases), the latency to the first pellet delivery of the first meal (including the time required to complete the first meal appetitive phase), the number of light presentations during the first appetitive phase, the number of food pellets earned during the first consumption phase, and the running rate (responses/s timed from the first response after reinforcer delivery to the next reinforcer delivery) during the first appetitive and consumption phases of each session were calculated. Data for each drug were summarized using analyses of variance (ANOVA) with Sex as a between group factor and Drug (placebo vs. active; there was one placebo session for each active dose session), and Dose (4 or 2 doses) as 2-within group factors. Data were considered significantly different at $P<0.05$.

Data for each drug dose were graphed as change from the non-drug data usually collected on the day prior to the drug day. By controlling for baseline changes, a significant Drug × Sex effect can be visualized as a significant effect of Sex, a significant Drug × Dose effect can be visualized as a significant effect of Dose, and a significant Drug × Dose × Sex effect can be visualized as a significant interaction between Dose and Sex, i.e., ANOVAs using change scores yield the same values as ANOVAs using baseline as a covariate.

3. Results

Under baseline conditions, baboons started the first consumption phase, i.e., meal, of the day about 2 h after the start of the session, had about 4 meals (consumption phases) each session, earned about 70 light presentations, i.e., baboons responded about 700 times during appetitive phases, and ate about 200 food pellets, i.e., baboons responded about 2000 times during consumption phases.

There was a trend ($P<0.055$) for males (201±8.9) to eat more food pellets than females (148±14.4) each day. There was a significant main effect of drug [$F(1,6)=11.71$, $P<0.014$] on food intake. Baboons ate significantly less food when they received baclofen (146±14.7), collapsed across doses, compared to placebo (203±8.2). As shown in the upper left panel of Fig. 1, baclofen produced dose-dependent decreases in pellet intake [$F(3,18)=6.04$, $P<0.005$]: at the largest baclofen dose, baboons ate about 150 fewer pellets. Baboons received significantly fewer stimulus presentations during appetitive phases [$F(1,6)=11.01$, $P<0.016$] when they received baclofen (55±7.2) compared to placebo (82±7.1). As shown in the lower left panel of Fig. 1, in contrast to consummatory behavior, the effects of baclofen on appetitive responding were not dose-dependent ($P<0.06$).

There was a trend ($P<0.058$) for males (106±8.4 min) to begin eating sooner than females (184±22.9) each day. As shown in the upper right panel of Fig. 1, latency to the first meal increased with increasing baclofen dose [$F(3,18)=4.13$, $P<0.021$]. Males (4.2±0.2) had significantly more meals than females (2.9±0.2) each day [$F(3,18)=4.13$, $P<0.021$]. There was a significant main effect of drug [$F(1,6)=6.8$, $P<0.04$] on the number of meals. Baboons had significantly fewer meals each day when they received baclofen (3.2±0.3), collapsed across doses, compared to placebo (3.9±0.2); but the effect was not dose-dependent ($P<0.08$).

Baclofen did not alter the number of light presentations during the first appetitive phase, the rate of responding during the first appetitive phase, the number of pellets earned during the first meal, nor the rate of responding during the first meal (lower right panel of Fig. 1). Although there were several differences between males and females in baseline eating behavior, there were no significant differences between males and females in the effects of baclofen on appetitive or consummatory behavior. Most baboons showed symptoms of

discomfort, e.g., slouching, following the 5.6 mg/kg dose and 2 females and 2 males vomited in the morning.

There was a significant main effect of drug [$F(1,6)=29.1$, $P<0.002$] on food intake. Baboons ate significantly more food when they received diazepam (251±18.6), collapsed across doses, compared to placebo (182±18.4). As shown in the upper left panel of Fig. 2, diazepam produced dose-dependent increases in pellet intake [$F(1,6)=11.4$, $P<0.015$]: baboons ate up to 120 more pellets when they received diazepam. There was a trend for baboons to receive significantly more stimulus presentations during appetitive phases [$P<0.07$] when they received diazepam. As shown in the lower left panel of Fig. 2, baboons received about 50 more stimulus presentations after they received diazepam compared to placebo.

There was a significant main effect of drug [$F(1,6)=5.9$, $P<0.05$] on the latency to the first meal. The latency to the first meal of the day was significantly shorter when baboons received diazepam (57±8.7), collapsed across dose, compared to placebo (80±9.4). As shown in the upper right panel of Fig. 2, this effect was dose-dependent [$F(1,6)=9.6$, $P<0.02$] with latency being decreased only by the smaller diazepam dose. There was a trend ($P<0.06$) for males (4.7±0.3) to have significantly more meals than females (3.3±0.3) each day. Diazepam did not affect meal number.

Diazepam did not alter the number of stimulus presentations received during the first appetitive phase, but did there was a significant main effect of drug [$F(1,6)=13.2$, $P<0.011$] on the number of food pellets earned during the first meal. Baboons consumed more food during the first meal when they received diazepam (103±13.2), collapsed across doses, compared to placebo (56±9.4). Diazepam did not affect rate of responding during the first appetitive component nor the first meal (bottom right panel of Fig. 2). As with baclofen, there were no significant differences between males and females in the effects of diazepam on appetitive or consummatory behavior. Finally, all baboons showed signs of sedation following the larger diazepam dose.

4. Discussion

The results of the present study provide no evidence that baclofen increases food consumption in non-human primates. In fact, the two largest baclofen doses decreased food consumption. The decreases were accompanied by visual signs of discomfort and emesis in half of the baboons, indicating that the effect was most likely due to non-specific malaise. These findings are in contrast to the commonly reported food-consumption increasing effect of baclofen when administered centrally or peripherally to rats (Ebenezer, 1995; Ebenezer and Pringle, 1992; Stratford and Kelley, 1997; Ward et al., 2000). The decreased food intake replicates another study that gave baclofen to baboons (Weerts et al., 2005). Although Weerts et

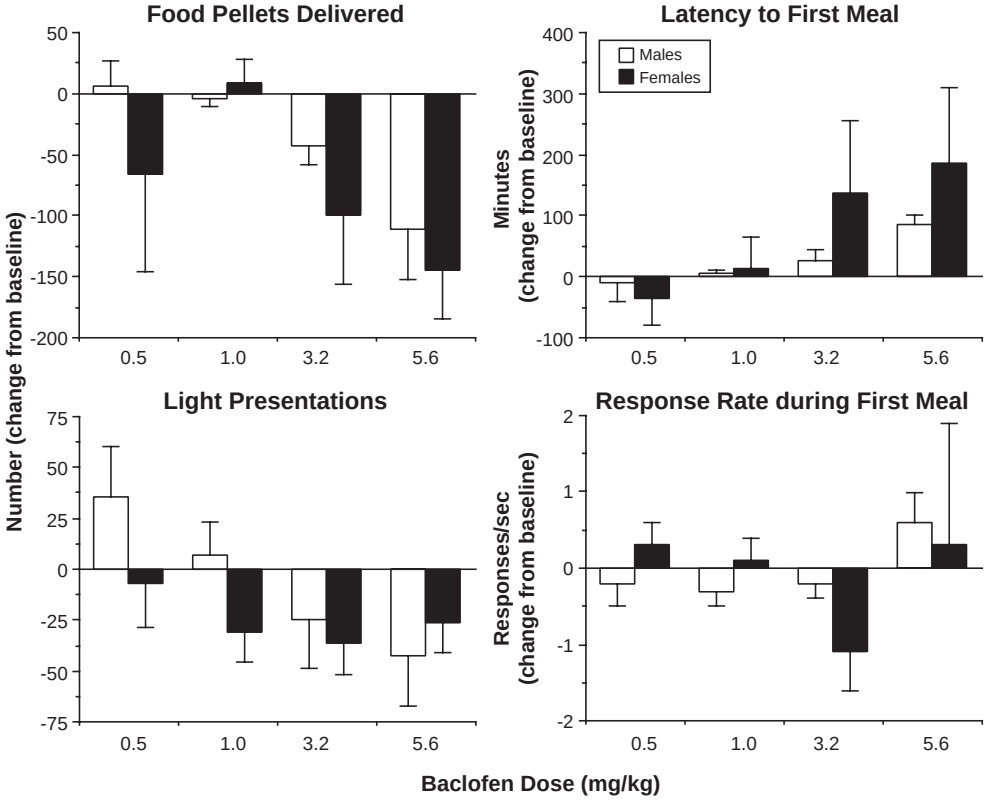

Fig. 1. Top left panel: Mean change in daily number of food pellets delivered during the entire session as a function of baclofen dose. Bottom left panel: Mean change in daily number of light presentations delivered during appetitive phases for the entire session as a function of baclofen dose. Top right panel: Mean change in latency to the first meal as a function of baclofen dose. Bottom right panel: Mean change in response rate during the first meal of the session as a function of baclofen dose. Error bars represent 1 SEM.

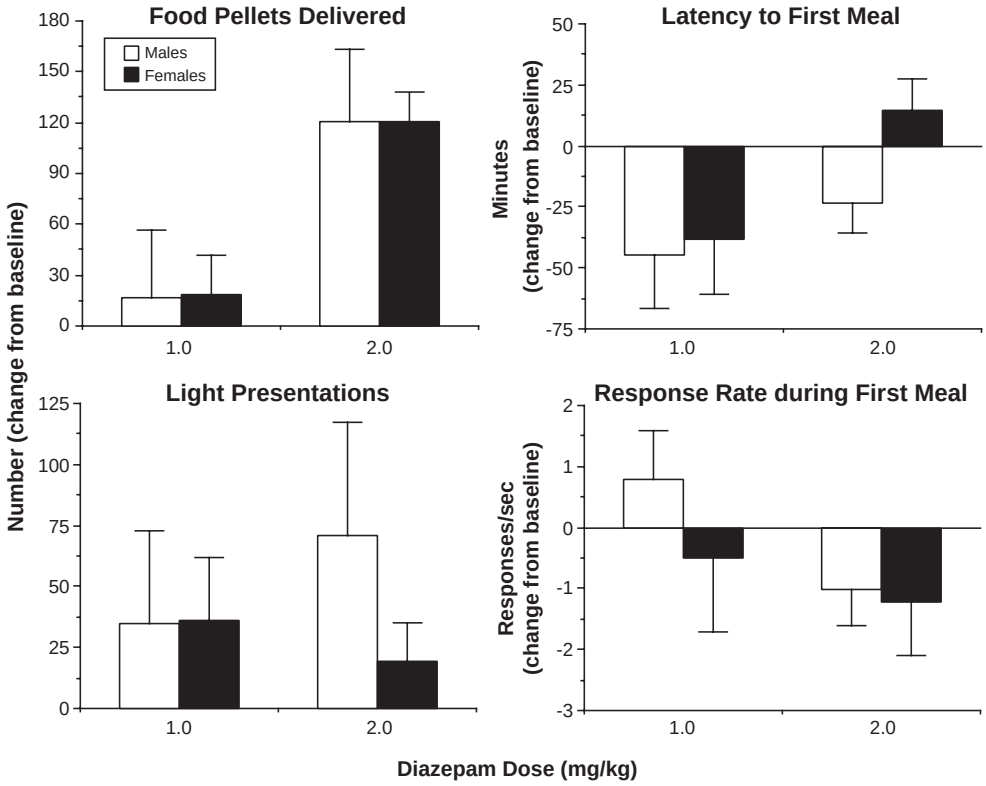

Fig. 2. Top left panel: Mean change in daily number of food pellets delivered during the entire session as a function of diazepam dose. Bottom left panel: Mean change in daily number of light presentations delivered during appetitive phases for the entire session as a function of diazepam dose. Top right panel: Mean change in latency to the first meal as a function of diazepam dose. Bottom right panel: Mean change in response rate during the first meal of the session as a function of diazepam dose. Error bars represent 1 SEM.

al. (2005) did not mention significant side effects in their report, Tarika and Winger (1980) did report significant sedation in rhesus monkeys. In humans, the most common side effects of baclofen are drowsiness and weakness, but nausea and vomiting are also possible. Because the significant side effects in half of the animals undoubtedly influenced study outcome, the current results may not provide information about how GABAergic systems are involved in feeding behavior.

The results of the present study indicate that baclofen decreases appetitive behavior: latency to the first meal was increased and responding during appetitive components was decreased by the largest baclofen doses. Di Ciano and Everitt (2003) have also reported baclofen increased latency and decreased responding under second-order schedules, as used here, of heroin and cocaine self-administration in rats. Colombo et al. (2003) reported that baclofen decreased responding by rats under extinction conditions, further supporting the hypothesis that baclofen decreases appetitive behavior. Thus, the present findings partially confirm data obtained in rodents, with the caveat that non-specific malaise may have contributed to the behavioral changes.

The effects of diazepam in the current study more closely mirror previous studies in non-human primates and rats. Diazepam increased both appetitive and consummatory behavior: latency to the first meal was decreased and responding during consummatory components was increased by diazepam. Because a different anxiolytic chlordiazepoxide had no effect on responding reinforced by stimuli paired with water reinforcement under extinction conditions (Robbins et al., 1983), the increase in appetitive behavior is most likely due to an increase in motivation to eat (Bielajew and Bushnik, 1994; Cooper and Estall, 1985; Foltin, 1993), rather than an increase in the reinforcing effects of stimuli paired with food. Baclofen, on the other hand, has been hypothesized to specifically decrease the effects of stimuli paired with primary reinforcement (e.g., Franklin and Druhan, 2000; Yun et al., 2004).

Changes in feeding topography support the assertion that baclofen had non-specific effects on food intake. Baclofen increased the latency to the first meal and decreased the number of meals without affecting responding or response rate during the first appetitive or consumption component of the day. This suggests that malaise (based on the presence of emesis) induced a pause in feeding. In contrast, diazepam decreased the latency to the first meal, had no effect on the number of meals, but nearly doubled responding during the first consumption component of the day, without affecting response rate. Although baclofen had no effect on rate of responding once responding began, two studies have reported that baclofen decreases rate of responding (Munzar et al., 2000; Negus et al., 2000) in rats and rhesus monkeys.

Nearly all previous studies have used male laboratory animals (~90% of the papers in reference section). Several studies report using male and female animals in the paper, but did not mention any possible effects of sex (Ebenezer and

Baldwin, 1990; Reynolds and Berridge, 2002). One paper used female rats exclusively, and failed to find an effect of centrally administered baclofen on food intake, although central administration of the $GABA_a$ agonist muscimol did increase food intake (Minano et al., 1992). We found no evidence for a consistent effect of sex on the response to baclofen or diazepam. It is possible that sex differences exist, but were not observed, however, because the females were just reaching maturity, i.e., beginning to experience sexual swelling and menarche.

The effect of baclofen on feeding behavior across studies has been variable. While most studies report that central or peripheral baclofen increases food intake (e.g., Ward et al., 2000), one reports that central, but not peripheral baclofen increases food intake (Ebenezer and Baldwin, 1990), while others report that baclofen, in similar dose ranges, has no effect (e.g., Jonaidi et al., 2002), or decreases food intake (e.g., Addae et al., 1986; Zarrindast et al., 1989). A further complication to studying the effects of baclofen on feeding behavior is the fact that baclofen can increase oxygen consumption (Horton et al., 1988), body temperature, metabolic rate and the thermogenic activity of brown adipose tissue (Addae et al., 1986), all of which may affect feeding behavior. Finally, baclofen may alter the effects of stimuli paired with primary reinforcement in guiding appetitive behavior (e.g., Di Ciano and Everitt, 2003). Thus, baclofen produces a wide variety of effects and subtle differences in methodology are likely to differentially influence the sensitivity of the procedure to these effects and greatly affect study outcome.

This study has several significant limitations. The fact that doses were tested in an ascending order with all animals getting the same dose each test day may have affected the outcome. Each dose was also tested only once. Because the effects of acute administration may not reflect the effects of repeated administration, future work should examine repeated dose regimes. An approach that uses small initial doses and gradual dose escalation may limit side effects and provide information about the specific effects of baclofen on feeding behavior. Finally, although no sex differences were observed here it is possible that sex effects would be evident with a larger sample size and more mature animals.

In summary, the peripheral administration of the $GABA_a$ agonist diazepam increased appetitive and consummatory behavior in baboons, while the peripheral administration of the $GABA_b$ agonist baclofen decreased appetitive and consummatory behavior in baboons, with at least part of baclofen's effect accounted for by non-specific behavioral disruptions. Future work with baclofen, especially in non-human primates, needs to carefully assess the behavioral specificity of the hypothesized action of baclofen.

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