THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF NUTRITIONAL SCIENCES

INTRAPERITONEAL ADMINSTRATION OF BACLOFEN FAILS TO REDUCE INTAKE OF FAT EMULSIONS LACKING STARCH IN RATS

DANIELLE C. WILT

Fall 2009

A thesis
submitted in partial fulfillment
of the requirements
for a baccalaureate degree
in Science
with honors in Nutritional Sciences

Reviewed and approved* by the following:

Rebecca L. Corwin
Associate Professor of Nutritional Neuroscience
Thesis Supervisor & Honors Advisor

Gary J. Fosmire
Associate Professor of Nutritional Sciences
Faculty Reader

*Signatures are on file in the Schreyer Honors College.

Abstract

The $GABA_B$ agonist baclofen generally reduces intake of high-fat diets and stimulates or has no effect on the intake of other foods. The present study tested the effects of baclofen on intake of emulsions containing fat at concentrations found in foods commonly consumed by humans. Non-food deprived Sprague-Dawley rats were given 1-hour access five days a week to corn oil or vegetable shortening emulsions of 1%, 3.2%, 10%, and 32% fat concentration. Emulsions were either liquid, or were thickened with Ticalose CMC 6000 (Tic), which contains no starch. Effect of baclofen on intake of 100% vegetable shortening was also determined in order to assess drug efficacy. Baclofen (0.6, 1.0, 1.8 mg/kg) or its vehicle (saline) was administered intraperitoneally and its effects on intake of fat emulsions and 100% vegetable shortening determined. Results indicated that baclofen had no effect on the intake of most of the fat emulsions. However, baclofen stimulated intake of the 3.2% corn oil emulsion with 0% Tic (a liquid emulsion) and 10% vegetable shortening with 2% Tic (a solid emulsion) at the 1.0 mg/kg and 1.8 mg/kg doses, respectively. Baclofen decreased intake of 100% vegetable shortening. No consistent findings related to concentration of fat or consistency of emulsions emerged. Previous research from this laboratory had shown that baclofen reduced intake of a 32% vegetable shortening emulsion thickened with a starch-containing Tic product (Rao et al., 2008). In contrast, the thickeners used in the present study lacked starch, which may account for the different results. These findings suggest that the ability of baclofen to reduce the intake of fatty food may depend upon the fat concentration, as well as other components of the food that contribute to its palatability.

Table of Contents

Acknowledgements

I would first like to thank Dr. Rebecca Corwin and Dr. Francis Wojnicki for all of the time and effort they put into my research endeavors. I continue to be amazed by their kindness and dedication to their field. My experience in their lab has taught me so much and the lessons learned will continue to benefit me for the rest of my life. Furthermore, I want to show my appreciation for Dr. Gary Fosmire, who generously agreed to be the faculty reader. Finally, I want to express my deepest gratitude to my family, especially my parents. Their constant outpouring of love and support has allowed me to pursue my dreams.

Introduction

The United States of America has become a nation of expanding waistlines. A survey that examined the body mass index of adults in 2005-2006 found some disturbing results among Americans. In the 20-74 age range, 32.2% were overweight, 35.1% were obese, and 6.2 % were morbidly obese. Thus, 73.5% of the American population is not at a healthy weight (WHO, 2008). One important reason for this phenomenon is thought to be the 63% increase in total per capita consumption of fats and oils that occurred between 1970 and 2003 (Farah & Buzby, 2005). Despite the mid-1990's campaign to reduce dietary fat, these added fats and oils were responsible for an extra 216 calories per person per day when considering the data from 1970 to 2003 (Farah & Buzby, 2005). If an individual consistently consumed these additional 216 calories per day, it would result in a 22 lb weight gain over the course of a year. These statistics are alarming due to the numerous diseases that are associated with excess body weight. They include diabetes type 2, ischaemic heart disease, stroke, hypertensive disease, osteoarthritis, and cancer (colon, kidney, endometrial and postmenopausal breast cancer) (WHO, 2008). The most lethal of these illnesses is heart disease, which resulted in more than 864,000 fatalities in the U.S. in 2005, or 35.3% of all deaths (AHA, 2009). The American Heart Association also reported that as of 2006, 80 million or 1 in 3 Americans suffer from one or more type of cardiovascular diseases. Obviously the American diet is in need of restructuring, yet people continue to consume more fat than ever. The high palatability of fat and its role in obesity merit investigation.

It is important to understand the molecular structure and properties of fat when discussing its effects. Fat consists of one to three fatty acids linked by ester bonds to a glycerol side chain. The fatty acids are carboxylic acids that are comprised of hydrocarbon chains of varying length. The combination of three fatty acids and glycerol is termed a triacylglycerol. These hydrocarbon

chains can be saturated and contain no double bonds, or be unsaturated and have one to several double bonds. The degree of saturation refers to the number of double bonds present in these fatty acid hydrocarbon chains. If no double bonds are present then the fatty acid is saturated, while one or more double bonds constitute an unsaturated fatty acid. Most fats that are in vegetable oils are mixtures of triacylglycerols with differing degrees of fatty acid saturation. The number of double bonds in the fatty acids is directly proportional to the fluidity of the oil. A greater number of double bonds in fatty acids will cause an oil to be more liquid. Thus, corn oil with its high concentration of unsaturated fatty acids is liquid at room temperature. Conversely, vegetable shortening is more saturated with a smaller number of double bonds; therefore, it is a solid. Moreover, the double bonds present in fats are capable of being oxidatively cleaved when exposed to the oxygen in air. The result is a rancid smell and taste (Nelson & Cox, 2009).

While fat is known to have satiating properties, it also can have powerful rewarding properties (Sclafani, 2004a). Numerous studies, for instance, have demonstrated that fatty foods are favored by both humans and rats (Drewnowski et al., 1989; Drewnowski & Greenwood, 1983; Lucas et al., 1989). These preferences could be the result of how fat is perceived when it is consumed. Fat can be detected via olfactory, gustatory, and postingestive signals. The role for olfactory signaling in fat palatability has been shown in some studies with mice and rats (Kinney & Antill, 1996; Ramirez, 1993c). However, the attractiveness of fat seems to not be completely dependent upon smell, since it has been shown that rats will continue to eat fat even when they are anosmic (Fukuwatari et al., 2003; Takeda et al., 2001).

One important discovery regarding the gustatory aspects of fatty acid detection and preference was that of an integral membrane lipid-binding protein on the tongue termed CD36.

This receptor is thought to be specific to the detection of fat. Mice that were CD36-deficient no longer consumed a palatable long-chain fatty acid solution, while their preference for a sucrose or quinine solution was unaffected (Laugerette et al., 2005). Additionally, activation of the brain stem by linoleic acid in the mouth is probably CD36 dependent in mice. Mice that had CD36 intact showed stimulation of this brain area by oral linoleic acid (Gaillard et al., 2008), while those with an abolished receptor did not. Finally, mice that were lacking CD36 showed decreased fat consumption compared to their CD36-intact counterparts (Sclafani et al., 2007).

Conversely, the mechanism by which texture contributes to the palatability of fat is variable and uncertain. It appears that texture is a construct that is relevant to the detection of fat but is not the sole contributor. Specific regions of the brain are activated in the brain due to the viscosity of stimuli in the oral cavity (de Araujo et al., 2004). Modifying the texture of a substance can also obscure its perceived fat content. Human subjects had difficulty properly reporting the fat content of solid foods and dairy foods modified with textural agents to have similar viscosities (Drewnowski et al., 1989; Mela, 1988). Corn oil and mineral oil possess a similar texture, yet mineral oil is composed of *n*-alkanes and some cyclic paraffins (WHO, 1970). Both corn oil and mineral oil will stimulate sham-feeding in rats when given individually. However, when rats are given the opportunity to choose, they prefer corn oil to mineral oil (Mindell et al., 1990; Smith & Greenberg, 1991). Others also have shown that the fat content of an emulsion can affect intake independent of viscosity (Mela et al., 1994). Taken together, these reports indicate that texture is not the only property of fatty foods mediating palatability.

The fatty acid profile and nutrient composition of fats can also lead to different preferences in rats (Ackroff et al., 1990; Ackroff et al., 2005; Elizalde & Sclafani, 1990; Lucas et

al., 1989; Ramirez, 1992; Rice et al., 2000). One study found that rats prefer fats with a lower saturated fatty acid and/or higher polyunsaturated fatty acid content (Ackroff et al., 2005). It was also found that the linoleic acid content of the fat source can affect the reinforcing properties of the fat. This result led the authors of the study to speculate that corn oil, followed by vegetable shortening, and then beef tallow would be preferred by virtue of their linoleic acid content (Ackroff et al., 2005). It appears that it is not one distinguishable aspect of fat that makes it so irresistible, but rather a combination.

After fat is sensed in the mouth or intestinal tract, a variety of neural circuits is activated. The brain areas that are stimulated could provide a rationale into why fat is unable to be resisted in spite of its negative health consequences. Research has shown that the parabrachial nucleus and lateral hypothalamus participate in the processing of gustatory cues of palatable food (Ferssiwi et al., 1987; Sclafani et al., 2001; Touzani & Sclafani, 2001). Moreover, fat is involved in the activation of receptor signaling in areas of the brain associated with reward (Bassareo et al., 2002; Buda-Levin et al., 2005; de Araujo & Rolls, 2004; Sawano et al., 2002; Verhagen et al., 2003; Verhagen et al., 2004). Specifically, the mesolimbic dopamine system is thought to be involved in the rewarding effects of food. For example, sham-feeding corn oil is capable of causing the release of dopamine into the nucleus accumbens in rats (Liang et al., 2006). An additional study observed that decreased central dopamine due to polymorphisms in humans is related to intensified desires for palatable foods (Sobik et al., 2005). It has been hypothesized that the psychological desire and drive for highly palatable fatty food is as strong as the physiological response to eat due to energy deprivation (Lowe & Levine, 2005). Indeed, it has been shown that in a binge-model of eating, rats will consume fat even when they are not energy-deprived (Buda-Levin et al., 2005; Corwin et al., 1998). Similar neural systems have been

implicated in binge-eating disorders and drug addiction, both of which involve behaviors that are detrimental to good health.

The neural circuits involved in the rewarding properties of fat and drugs have been researched extensively because they offer important insights into why a person will overeat certain foods or abuse drugs. If a neural etiology is determined, then it would be possible to pharmacologically attenuate cravings for high-fat palatable foods. One neurotransmitter that has been implicated in both drug addiction and fatty food intake is γ-aminobutyric acid (GABA) (Billinton et al., 2001; Blein et al., 2000). GABA is the main inhibitory neurotransmitter in mammalian central nervous systems (Cooper et al., 2003). Two types of GABA receptors exist in the brain, $GABA_A$ and $GABA_B$. These are functionally distinct receptors that modulate different outcomes. The $GABA_A$ receptors are targets of sedative drugs such as benzodiazepines and barbiturates (Cooper et al., 2003). $GABA_B$ receptors have been linked to a myriad of addiction-related behaviors (Ariwodola & Weiner, 2004; Cousins et al., 2002; Roberts, 2005). There are numerous effects that GABA exerts; one of which is the attenuation of dopamine neurotransmission (Klitenick et al., 1992; Santiago et al., 1993a & b). For instance, one study demonstrated that GABA attenuated cocaine-stimulated dopamine release in the nucleus accumbens and corpus striatum in rats (Dewey et al., 1997).

The study of the role of $GABA_B$ receptors in drug and food intake has been facilitated by the use of a $GABA_B$ agonist called baclofen. Baclofen is capable of crossing the blood brain barrier unlike other $GABA_B$ agonists such as 3-APA (Ebenezer & Patel, 2004). Thus, baclofen can be administered systemically and still affect the central nervous system. Although the behavioral effects of baclofen are thought to be primarily centrally mediated, baclofen can also have direct effects upon the vagus nerve and gut (Goto et al., 1985; Partosoedarso et al., 2001).

Baclofen also increases oxygen consumption (Horton et al., 1988), body temperature, metabolic rate, and thermogenic activity of brown adipose tissue (Addae et al., 1986). At higher doses, it is a skeletal muscle relaxant that has been used to treat the spasticity associated with multiple sclerosis and cancer specific neuropathic pain (Sadiq & Poopatana, 2007; Yomiya et al., 2008).

Numerous studies using baclofen have been performed in many species in which its ability to alter drug and food intake have been examined. Baclofen decreased drug self-administration in most studies. For example, baclofen reduced the intake of cocaine (Brebner et al., 2002), *d*-amphetamine (Brebner et al., 2005), methamphetamine (Ranaldi & Poeggel, 2002), ethanol (Stromberg, 2004), nicotine (Paterson et al., 2004), and heroin (DiCiano & Everitt, 2003). Baclofen is thought to act in the brain to exert its effects; when injected into the ventricles or directly into the nucleus accumbens, it decreases the self-administration of cocaine as well as behaviors associated with the cocaine (Dewey et al., 1997). In addition, baclofen caused a decrease in the release of dopamine in the ventral tegmental area (Klitenick et al., 1992).The effects on behavior may be due to baclofen's effects on dopamine neurotransmission; baclofen inhibited a mesolimbic dopamine release associated with heroin (Xi & Stein, 1999).

Conversely, the effects of baclofen on food intake vary, which is probably due to differences in the types of food and protocols utilized. Baclofen increased intake of a solid food in rats (Ebenezer, 1995; Ebenezer & Patel, 2004; Ebenezer & Prabhaker, 2007; Ebenezer & Pringle, 1992; Echo et al., 2002; Patel & Ebenezer, 2008a & b; Ward et al., 2000) and stimulated feeding in satiated pigs (Ebenezer & Baldwin, 1990). In addition, rats ran faster in a runway to obtain a food reward after baclofen; however, intake itself was not affected (Higgs & Barber, 2004). In contrast, others have shown that baclofen either has no effect on or decreases the intake

of solid food in animals (Foltin, 2005; Paterson et al., 2004; Smith et al., 1999; Zarrindast et al., 1989) In spite of these results, the studies that showed reductions in intake gradually utilized high doses of baclofen that are capable of non-specific behavioral disruptions such as sedation. More research is needed that involves standardized protocols to make comparisons among food intake studies possible.

Given the similarity between neuronal substrates mediating the rewarding effects of drugs of abuse and palatable foods, some studies have examined whether baclofen would also reduce the intake of fat or sucrose. Several studies have focused upon fat intake in rats when they are placed in binge-type conditions. Corwin and Buda-Levin (2004) outlined a model of limited access to fat that induces binge-type eating that could be loosely compared to binge-related disorders in humans. While it is an imperfect model because of innate differences between humans and rats, it demonstrates face and construct validity and is relatively simple to use (Corwin & Buda-Levin, 2004). Some studies have revealed that baclofen decreased fat intake when rats were placed in these binge-type conditions (Berner et al., 2009; Buda-Levin et al., 2005; Rao et al., 2008; Wojnicki et al., 2006;). Baclofen has also been shown to decrease the number of binge eating episodes in humans with binge-related disorders in an open-label trial (Broft et al., 2007). Nevertheless, when rats were placed in more of a “non-binge” protocol that involved daily access, decreases in fat intake were also observed (Corwin & Wojnicki, 2009; Rao et al., 2008; Sato et al., 2007; Wong et al., 2009). The effects of baclofen on consumption of sweet liquids that include ingredients like sucrose or saccharin are mixed. Baclofen increased intake of a sweet solution in one study (Ebenezer, 1995), while the majority of the literature has indicated no effect (Avena et al., 2009; Berner et al., 2009; Corwin & Wojnicki, 2006; Corwin & Wojnicki, 2009; Ward et al., 2000) Studies with baclofen on intake of sucrose and fat

combinations show mixed results depending on the concentrations of each component used. A study by Wong et al. (2009) showed that baclofen would decrease intake of fat emulsions with 3.2% and 10% powdered sugar whipped into it, yet had no effect on fat emulsions with 32% powdered sugar. Likewise, baclofen had no effect on the intake of a sweet-fat chow that was 45% fat and 35% carbohydrate (Berner et al., 2009). Therefore, it appears that the type of food consumed modulates the effects of baclofen. The available evidence suggests that fat intake is particularly sensitive to the intake-reducing effects of baclofen.

The research conducted for this thesis sought to examine how baclofen affects the intake of liquid and solid fats in concentrations significantly lower than those previously used. The focus upon fat rather than sucrose was due to recent research indicating that baclofen had no effect on sucrose intake (Avena et al., 2009; Berner et al., 2009; Corwin & Wojnicki, 2009). Prior research in regards to fat primarily utilized 100% vegetable shortening and demonstrated decreases with baclofen (Buda-Levin et al., 2005; Corwin & Wojnicki, 2009). However, Rao et al. (2008) showed decreases in consumption of a solid vegetable shortening emulsion consisting of 18%, 32%, 56% vegetable shortening in non food-deprived rats with 1-hour access each day to the emulsions. The present study sought to determine if similar results would be obtained with fat concentrations of 1%, 3.2%, 10%, and 32%. One reason for this modification is that the content of typical human high-fat foods ranges from ~18% (cookies and some ice creams) to ~32% (chocolate candy) by weight. Research using lower fat concentrations can better model the palatable food that humans consume. Both corn oil and vegetable shortening emulsions were used to see if baclofen would be equally effective in reducing intake of emulsions with different fatty acid profiles. Finally, the effects of baclofen on the intake of emulsions with different textures were explored with liquid and solid emulsions. As noted, baclofen stimulates the

$GABA_B$ receptors that are widely distributed throughout the central nervous system and thus also the regions specific to reward. By manipulating the qualities of fat that make it so irresistible and observing whether baclofen has an effect could lead to a specific identification of the role of $GABA_B$ receptors in fat-reward neural pathways. Such research could ultimately lead to the development of fat substitutes with reduced energy density. This alternative could perhaps function to decrease the energy intake of individuals and thus their tendency to become overweight or obese and reduce cardiovascular disease risk while still providing the rewarding properties that make fat so irresistible.

Methods

Emulsions

Throughout this study, corn oil emulsions, vegetable shortening emulsions, and pure vegetable shortening were used. All liquid corn oil emulsion concentrations (1%, 3.2%, 10%, and 32% w/v) were first mixed in a bovine sodium caseinate (Sigma Aldrich, St Louis, MO; 3.88 kcal/g) solution (1%) and coarsely homogenized in a high-speed mixer. The coarse emulsion was further homogenized using a two-stage valve homogenizer (1-5 passes, 200-500 bar, 10% of which was maintained over the second stage). The particle size distributions of corn oil emulsions were characterized by static light scattering and remained stable over the course of their use.

All solid corn oil emulsion concentrations were first prepared as liquid emulsions as described above. Once the liquid emulsions were homogenized, 2% w/v of Ticalose CMC 6000 (Tic Gums, Belcamp, MD) thickener was added to the liquid emulsion, mixed with a hand blender for 2 minutes, heated to 85°C for 2 hrs and then refrigerated. At room temperature all solid corn oil emulsions had the consistency of pudding. Ticalose CMC 6000 (Tic) contained microcrystalline cellulose, agar, and xanthan gum. Due to the indigestible cellulose, it had 0 g metabolizable energy and per 100 g consisted of 7,943 mg sodium, 19 mg potassium, 9 mg calcium, and 80 g of total carbohydrate (80 g soluble dietary fiber, 0 g insoluble dietary fiber, 0 g simple carbohydrate, 0 g complex carbohydrate).

Solid vegetable shortening (Crisco All-Vegetable Shortening, J.M. Smucker Co., Orrville, OH; 9.17 kcal/g) emulsions (1%, 3.2%, 10%, 32%) were prepared in the same manner

as the solid corn oil emulsions except that it was necessary to first pre-heat the oil and the homogenizer prior to use to ensure the lipid was liquid during homogenization.

Both corn oil and vegetable shortening emulsions were kept refrigerated. All emulsions were allowed to reach room temperature prior to administration. Emulsions left in the jar after feeding were discarded and new batches of emulsions were prepared weekly.

When 100% solid vegetable shortening was used, it was always kept at room temperature and given to the rats in the same manner as the emulsions. Fresh solid vegetable shortening was provided at the beginning of each week.

Animals

Forty male Sprague Dawley rats (Harlan, Indianapolis IN), 180 days of age, and weighing 399-509 g (465 ± 23.31 g) at the start of the study were used. They were housed individually in hanging stainless steel wire cages in a temperature- and humidity-controlled vivarium and relegated to a 12-hr light: 12 hr-dark cycle. Water and pelleted chow (Laboratory Rodent Diet 5001, PMI Feeds, Richmond, IN; 3.3 kcal/g) were available ad libitum. The chow composition provided by the manufacturer was: protein (28.05% of energy; 23.4% of weight), fat (12.14% of energy; 4.5% of weight), and carbohydrate (59.81% of energy; 49% of weight). One rat in the 1% corn oil emulsion group was euthanized due to health concerns not related to the study. Data from this rat were included in the initial analyses, during which time intake was unaffected.

Procedures

All animals were used in a previous experiment. In the former study, each group (n=10 each) was assigned to a specific corn oil concentration (1%, 3.2%, 10%, 32%) and kept at their respective corn oil concentration for the duration of the study. Animals had been assigned to their respective groups by being matched for body weight, average daily chow consumed over a 3-day period, and the amount of 5.6% canola oil emulsion consumed during one overnight period. While all animals were maintained on their respective corn oil concentrations, each group was exposed to emulsions containing different Tic concentrations (0% 0.5%, 1.0%, 1.5%, 2.0%, 2.5%) over a period of 3 months.

In the present study, each group was maintained on the corn oil concentration assigned to them in the previous study. Both the emulsions and 100% vegetable shortening were offered in glass jars of 6.5 cm in diameter and held stationary by stainless steel clips attached to the front of the cage for 1-h, starting 2 hours prior to the start of the dark cycle Monday through Friday.

The 0% Tic corn oil emulsions were first presented for 4 sessions. Thirty minutes prior to the 5^{th} session saline (i.p.) was administered as an adaptation to the injection procedure. Over the next two weeks the $GABA_B$ agonist (R-S)-baclofen; (0.0, 0.6, 1.0, 1.8 mg/kg, i.p., 30-min pretreatment) was administered on Mondays and Fridays, with Wednesdays serving as the baseline control.

The 2% Tic corn oil emulsions were next presented for 5 sessions. Baclofen was then administered over the following two weeks in the same manner as stated for corn oil emulsions with 0% Tic.

The vegetable shortening emulsions with the 2% Tic thickener were then presented to the rats over a 3-week period to establish a baseline. On the 16th and 20th sessions baclofen (0.0 and 1.8 mg/kg) was administered. The 1.8 mg/kg dose was chosen based on the results of previous work (Rao et al., 2008); this is a dose that does not induced non-specific behavioral disruption.

Finally, all rats were given a three-week adaptation period to 100% vegetable shortening. Baclofen (0 and 1.8 mg/kg, i.p.) was then administered.

Drug

The $GABA_B$ agonist (R-S)-baclofen (Tocris, Ellisville, MO) administered i.p. was dissolved in 0.9% saline in a volume of 1 ml/kg. The use of Monday and Friday as injection days allowed baclofen to be metabolized prior to subsequent injection. The Wednesday between the injections was utilized as a control day and no differences between Wednesdays indicated stable intake. For the corn oil testing doses were assigned to each rat using a uniform Latin square (0.0 (vehicle), 0.6, 1.0, and 1.8 mg/kg, 30-min pretreatment). For the vegetable shortening tests, only two doses were used (0.0 and 1.8 mg/kg); these doses were assigned to each rat in a counterbalanced manner. The doses were selected based upon previous reports of their effects on palatable food intake (Baker et al., 2001; Buda- Levin et al., 2005; Rao et al., 2007, Stein et al., 2000; Wojnicki et al., 2006, 2007; Wong et al., 2009), as well as a recent report describing effects on binge-type consumption of 100% vegetable shortening (Corwin & Wojnicki, 2009).

Statistics

SAS v. 9.1 (SAS Institute, Cary, NC) was used to analyze all data. For all 4 conditions (3-emulsions, as well as 100% vegetable shortening) baseline stability of intake was analyzed

using a 1-way repeated measures ANOVA and Tukey's HSD to determine differences across baseline days. An additional 1-way repeated measures ANOVA was used to assess differences between baseline and the first saline injection for the 0% Tic corn oil emulsions. The effectiveness of baclofen was assessed using a 2-way ANOVA (group X dose) for main effects and interactions. This was followed by a 1-way repeated measures ANOVA followed by Tukey's HSD, to assess differences among doses within each group. Baclofen data for the vegetable shortening tests were analyzed using paired t-tests (saline vs. 1.8 mg/kg). A 1-way ANOVA was used to analyze body weights amongst the groups at the start of each of the four conditions.

Results

Corn Oil Emulsions with 0% Tic

For the 0% Tic corn oil emulsions at all fat concentrations there were no significant differences between the 5th session saline day and any of the other 4 non-drug days that served as a baseline. With respect to baclofen administration, a 2-way ANOVA revealed there was a main effect of dose [$F(3, 108) = 5.50$; $p < 0.0015$] and corn oil concentration [$F(3, 36) = 3.72$; $p < 0.0199$], but no interaction. The main effect of dose and corn oil concentration was due to a significant increase in intake of the 3.2% corn oil concentration at the 1.0 mg/kg dose (Tukey's HSD, Fig. 1).

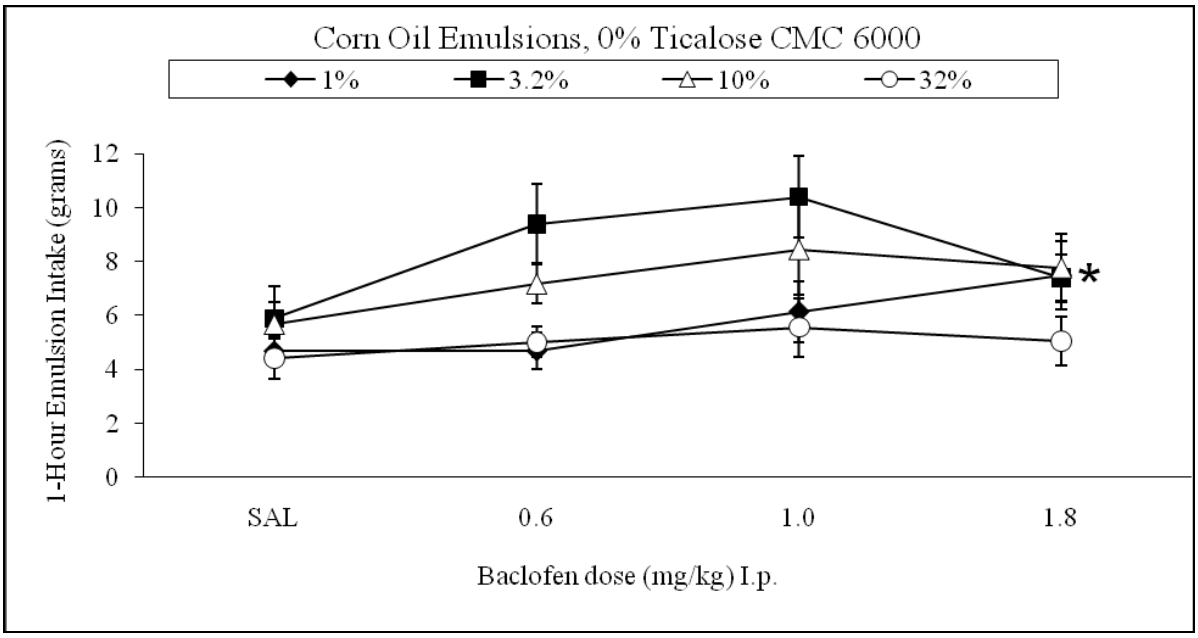

Fig. 1. Effects of baclofen on 1-hour intake of corn oil emulsions with 0% Tic. Asterisks indicate significant difference from saline ($p < 0.05$) and vertical lines represent standard error of the mean.

Corn Oil Emulsions with 2% Tic

For the 2% Tic corn oil emulsions, there were no significant differences in 3 of the 4 days during the baseline period, with the day that differed not being consistent among the groups. With respect to baclofen administration, a 2-way ANOVA revealed a main effect of dose [$F(3,108) = 3.09$; $p < 0.0302$] and concentration [$F(3,36) = 8.26$; $p < 0.0003$], but no significant interaction. The main effect of dose was due to a stimulatory effect of baclofen on intake at the higher doses. In spite of the main effect of baclofen dose (collapsed across all groups), 1-way ANOVA revealed no significant effects of baclofen at any of the doses within the individual groups. The main effect of oil concentration was due to differences in intake among the concentration groups (10% and 32% > 1% and 3.2%) at all doses as depicted in Fig. 2.

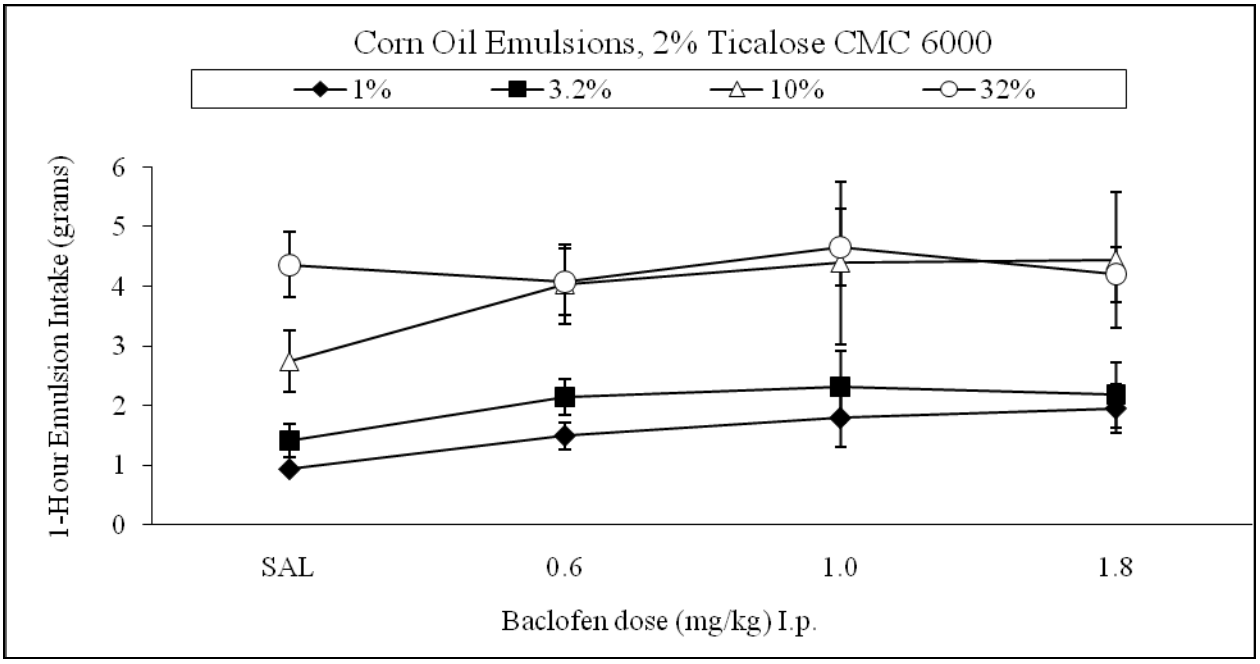

Fig. 2. Effects of baclofen on 1-hour intake of corn oil emulsions with 2% Tic. See Figure 1 for description of symbols.

Vegetable Shortening Emulsions with 2% Tic

For the 2% Tic vegetable shortening emulsions during the third week, there were no significant differences in shortening intake at any of the fat concentrations for 4 of the 5 days. With respect to baclofen administration, a 2-way ANOVA revealed a main effect of dose [$F(1,35) = 11.47$; $p < 0.0018$] and shortening concentration [$F(3,35) = 7.78$; $p < 0.0004$], but no interaction. The main effect of fat concentration was due to differences in intake among the groups (10% and 32% > 1% and 3.2%) at both doses (0.0 and 1.8 mg/kg). T-tests showed that baclofen caused a significant increase in consumption in the 10% shortening group ($p < 0.0189$, Fig. 3). All other groups showed no significant changes in intake due to baclofen.

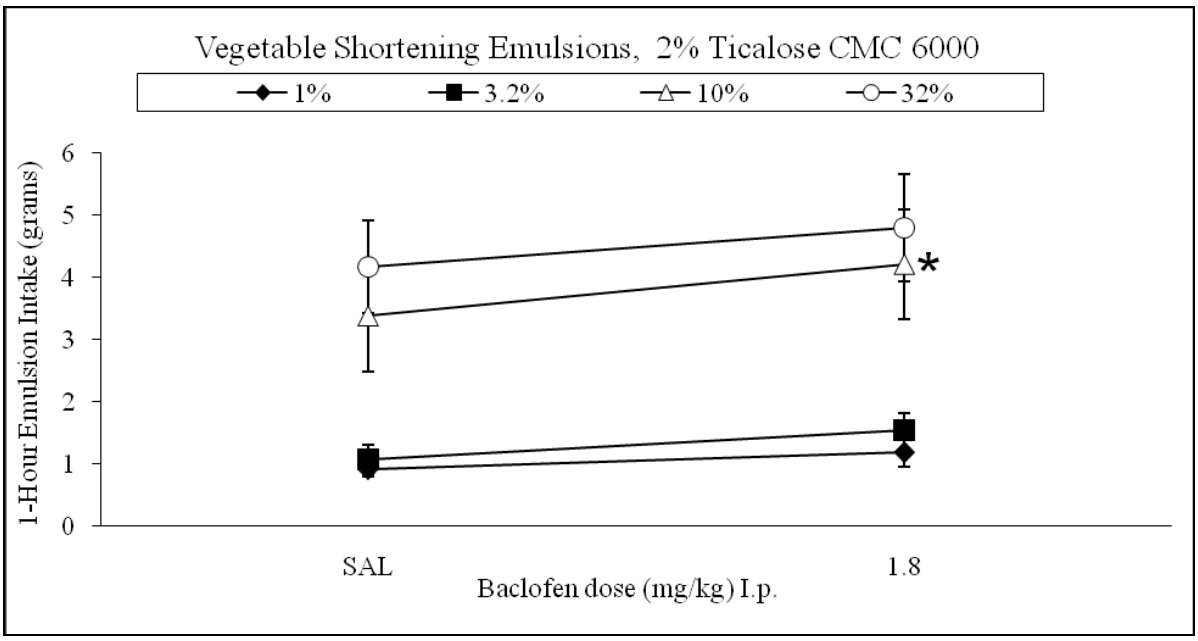

Fig. 3. Effects of baclofen on 1-hour intake of vegetable shortening emulsions with 2% Tic. See Figure 1 for description of symbols.

100% Vegetable Shortening

For the 100% vegetable shortening there were no significant differences in fat intake among any of the last 5 days of non-drug days. With respect to baclofen administration, a 2-way ANOVA revealed a main effect of dose [$F(1,35) = 26.22$; $p < 0.0001$], no main effect of former concentration group and no significant interaction. The main effect of dose was due to an inhibitory effect of baclofen on intake. T-tests for the individual groups indicated that baclofen caused a significant decrease in intake for both the former 3.2% and 10% fat concentration groups ($p < 0.0057$ and $p < 0.0188$, respectively, Fig. 4).

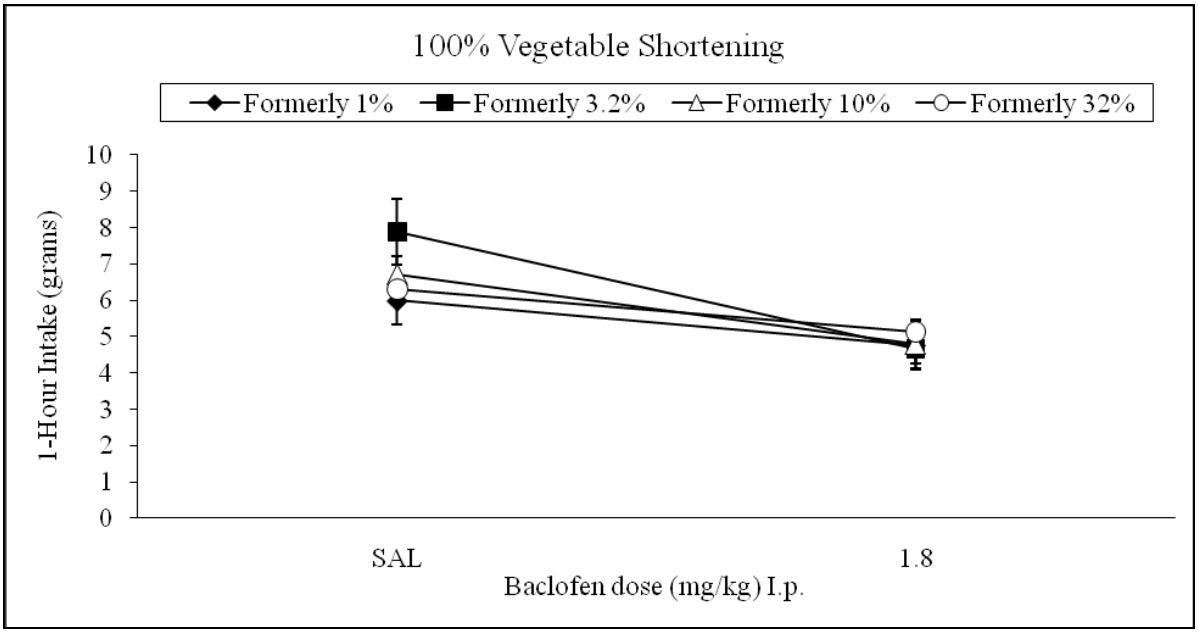

Fig. 4. Effects of baclofen on 1-hour intake of 100% vegetable shortening. See Figure 1 for description of symbols.

Body Weight

Body weights among the four groups at the start of each of the four conditions did not differ.

Discussion

The major finding of this report is that, with the exception of two emulsions, there were no significant effects of baclofen on intake of liquid or solid fat emulsions made with vegetable shortening or corn oil. The two exceptions were the 3.2% corn oil emulsion with 0% Tic, and the 10% vegetable shortening emulsion with the 2% Tic; baclofen stimulated intake of these emulsions at the 1.0 mg/kg and 1.8 mg/kg doses, respectively. Thus, the type of fat, concentration of fat, or texture of the emulsions did not predict baclofen efficacy. The present results are in striking contrast to previous reports in which baclofen reduced consumption of fatty foods. Specifically, baclofen decreased intake of 100% vegetable shortening (Buda-Levin et al., 2005; Corwin & Wojnicki, 2009), a high fat diet with 60% of calories from fat (Sato et al., 2007), solid fat emulsions of 18%, 32%, and 56% vegetable shortening (Rao et al., 2008), and vegetable shortening whipped with 3.2% and 10% powdered sugar (Wong et al., 2009).

The different results were not due to loss of drug activity. Efficacy of the drug was confirmed by the decrease in intake of the 100% vegetable shortening, while other emulsions showed no effect on intake or stimulation. The decrease in 100% vegetable shortening intake is consistent with other studies (Buda-Levin et al., 2005; Corwin & Wojnicki, 2009). The different results are also not likely due to the protocol used. Rats in the present study had access to the emulsions five days a week, whereas in previous reports access was provided daily or on Monday, Wednesday, and Friday of each week. Baclofen generally has comparable effects regardless of the fat access protocol when 100% vegetable shortening is used (Buda-Levin et al., 2005; Corwin & Wojnicki, 2009). When fat emulsions are provided, baclofen reduced intake of a 32% emulsion when it was provided daily, but had no effect when it was provided on Monday, Wednesday, and Friday (Rao et al., 2008). In no case did baclofen stimulate intake. Thus, while

the 5-day schedule utilized herein was different from those used in previous reports, it is unlikely that the protocol accounts for the discrepant findings. Finally, the present results are probably not due to the fat concentrations used. Baclofen reduced consumption of a 32% vegetable shortening emulsion in a previous report (Rao et al., 2008), but had no significant effect on either a 32% corn oil or vegetable shortening emulsion in the present study.

One difference between this and previous reports was the absence of starch in the thickener that was used. The current study utilized Ticalose CMC 6000, which lacks starch, whereas Rao et al. (2008) used Ticaloid 103-S Mayo, which contains starch. The final starch concentrations of the 18% and 32% emulsions in the Rao et al. (2008) study were 3.2% and 4.1%, respectively. Why baclofen would reduce intake of emulsions containing starch but have no effect on or stimulate intake of emulsions not containing starch is unknown. Starch consists of large glucose polymers that can be digested in the mouth and gut. As starch is digested, the linkages of glucose are broken down into the disaccharide maltose and the monosaccharide glucose. It has been proposed that starch-specific taste receptors exist (Sclafani, 2004b). Evidence for this includes the demonstration that preference for starch is not abolished by desalivation or removal of non-carbohydrate impurities from the starch (Ramirez, 1991a; Sclafani et al., 1987). Thus, it is not the digestion of starch by amylase in saliva or other components in the starch that are contributing to its palatability. Also, starch is not as soluble as a similar starch-derivative of water-soluble malto-oligosaccharides called Polycose. However, rats discriminate between the two carbohydrates and show a preference for starch over Polycose (Ramirez, 1991b; Sclafani et al., 1987). The rat's preferences demonstrate that starch is preferred even if a more soluble carbohydrate is available. Hence, if a receptor particular to starch detection is present, it is likely to have a high affinity for starch (Ramirez, 1991b).

Rats are capable of detecting starch in solution with concentrations as low as 0.025%. In addition, rats show a preference for solutions with starch compared to those lacking it (Ramirez, 1991a). Rats will consume corn starch robustly even when non-food deprived, demonstrating its acceptability (Ramirez, 1991a; Ramirez, 1993b; Sclafani et al., 1987). The effects of starch on intake are likely not due to its olfactory or textural qualities. For instance, one study showed that anosmic rats had a reduced, but intact preference for a 1% starch and oil suspension (Ramirez, 1993c). Additionally, rats trained to avoid substances with textural profiles similar to those of corn starch subsequently did not show a decreased preference for corn starch (Ramirez, 1993a), indicating that factors other than texture stimulate starch intake.

Taken together, the available evidence suggests that the presence of starch in the thickener used in the Rao et al. (2008) report may account for the different results obtained. Specifically, the presence of starch in the Rao et al. (2008) emulsions may have rendered them more palatable/rewarding than were the emulsions used in the present study. However, this theory is speculative since no controlled studies regarding the reward properties of starch relative to fat have been performed. It is then possible that if different foods are perceived as having different levels of reward, they may be acting via distinct neuronal pathways. This could be indicated by the fact that different neuronal systems are involved when food is consumed in response to homeostatic need rather than hedonic desire (Lowe & Levine, 2005). Homeostatic control of food intake is associated with regulation of energy balance. Hedonic systems, on the other hand, direct food intake based on the rewarding value of the food being consumed (Lutter & Nestler, 2009). Since $GABA_B$ receptors are present throughout the brain, their activation may differentially affect food intake mediated by these different systems. An example of this would be that the lateral hypothalamus and amygdala demonstrated greater degrees of activation when

human subjects orally consumed high-fat rather than low-fat drinks (Grabenhorst et al., 2009). Correspondingly, a high-fat diet is capable of upregulating the expression of five genes controlling the availability of dopamine in mice (Lee et al., 2009). It is proposed then that palatable food functions to overcome neuronal homeostatic control mechanisms and cause an animal or individual to be driven by hedonic desire (Berthoud, 2006). Thus, if starch is considered highly palatable/rewarding to a rat, it could be serving to activate predominantly hedonic neuronal pathways rather than homeostatic pathways. It is important to note that there is no marked divergence between homeostatic and hedonic pathways in the brain; rather, it seems there is interaction between the two (Lowe & Levine, 2005).

There are limitations in speculating that the inherent rewarding properties of starch make it capable of being affected by baclofen. Sucrose has been shown to be highly rewarding yet baclofen has no effects on consumption of sucrose solutions in concentrations of 3.2%, 10%, and 32% (Corwin & Wojnicki, 2009, Berner et al., 2009). Another relevant study is one by Wong et al. (2009) in which an increasing concentration of sucrose in conjunction with vegetable shortening attenuated baclofen's inhibitory effects on intake of fatty food. Baclofen decreased intake of fat emulsions with 3.2% and 10% sucrose, but at 32% sucrose showed no effect (Wong et al., 2009). It has been shown that starch and sucrose are detected and preferred differently by rats. The threshold concentration for the detection of starch is half that of sucrose (Ramirez, 1991b). It also has been shown that rats can discriminate between starch and sucrose solutions and will prefer the starch solution (Ramirez, 1991b; Ramirez, 1993b; Sclafani et al., 1987). While preference tests could possibly be an indication that starch is more rewarding than sucrose, it is essentially unknown how their effects on the reward pathways of the brain are modulated and differentiated from each other.

Therefore, we hypothesize that intake of fat emulsions lacking starch will operate predominantly by stimulating homeostatic control pathways. Perhaps then cholecystokinin (CCK), a key peptide involved in homeostatic control of meal size, could be involved (Dockray, 2009). The sites of CCK-releasing terminals have inhibitory presynaptic $GABA_B$ receptors (Raiteri et al., 1996). This could be the reason why baclofen is able to reduce the release of CCK-like material from rat spinal cords and CCK-like immunoreactivity from rat neostriatum (Benoliel et al., 1992; Conzelmann et al., 1986). Since baclofen is acting to attenuate the ability of CCK to induce feelings of satiety, it has been suggested that this is a possible mechanism by which baclofen stimulates food intake (Ebenezer, 1996). Such an effect could explain the well-documented stimulatory effect that baclofen has on chow intake (Ebenezer, 1995; Ebenezer & Patel, 2004; Ebenezer & Prabhaker, 2007; Ebenezer & Pringle, 1992; Echo et al., 2002; Patel & Ebenezer, 2008a & b; Ward et al., 2000) However, baclofen also attenuates dopamine release in brain reward areas (Klitenick et al., 1992; Xi & Stein, 1999). Since dopamine signaling is thought to be critical to brain reward processing, such an effect could result in reduced intake of foods that are consumed primarily for their rewarding properties, i.e. baclofen would render these foods less rewarding. For instance, sham-fed corn oil releases dopamine into the nucleus accumbens (Liang et al. 2006). Such an effect could explain why baclofen reduces consumption of optional fatty foods such as vegetable shortening, emulsions containing starch, and fatty foods containing relatively low concentrations of sucrose (Berner et al., 2009; Buda-Levin et al., 2005; Corwin & Wojnicki, 2009; Rao et al., 2008; Wong et al., 2009). Since the emulsions in the present study did not contain starch, it is possible that neuronal pathways relevant to homeostatic intake predominated and that the effects of baclofen were therefore mediated by those systems, rather than reward-related pathways. The tendency toward stimulation in the present report

supports this interpretation since CCK is more readily released in response to fats than in response to carbohydrates (Hopman et al., 1985; Lewis & Williams, 1990; Wells et al., 1997). Specifically, it was also found that fat and protein increase plasma CCK while starch does not (Hopman et al., 1985). The effects of starch could then be acting independently of CCK-mediated mechanisms and, rather, acting via reward pathways.

The textural aspects of the fat emulsions did not appear to play a significant role in the results. There were no well-defined trends in intake regarding the presence of Tic to thicken the emulsions. Texture is an element of fat that can be related to the perceived fattiness by the consumer (Mela, 1988; Mela et al., 1994). Nevertheless, texture is not the only aspect of fat that makes it detectable or palatable. Rats sham-feed 100% corn oil and 100% mineral oil, which is equivalent in texture to corn oil but nutritionally deficient. However, the rats still demonstrated preference for corn oil (Smith, Greenberg 1991, Mindell 1990). Additionally, oils consisting of similar fatty acid profiles were preferred differentially, which alludes to the possibility that orosensory mechanisms contribute to the preference of fats (Rice et al., 2000). The detection of fat in the mouth by receptors is complex and not well characterized. Nevertheless, some receptors in the oral cavity have been identified that strictly detect the presence of fat, viscosity of the substance, or both of these qualities (de Araujo 2004). Accordingly, the receptors modulating strictly fat would not be as stimulated by low-fat emulsions to arouse reward centers of the brain. Also, activations are produced by fat independent of its viscosity in the anterior cingulate region of brain. This region of the brain is also activated by sucrose; therefore, hedonic properties of fat independent of viscosity are possible (de Araujo 2004). The textural properties of the emulsions could possibly not be contributing a significant increase in the relative reward value to the extent that baclofen requires to be operational.

Relatively large gaps exist in the research involving the preference, reward value, and effects of baclofen on starch, fat, and sucrose. Controlled studies on the relative preference for these substances should be performed in the future. Likewise, more studies exploring various starch concentrations in fat could perhaps aid in explaining the results obtained in this study. A preliminary study that was completed in the Corwin lab hypothesized that the addition of starch to the same fat emulsions used in this study would reveal reductions in intake by baclofen. Indeed, the gradual addition of starch to the fat emulsions resulted in a decrease in intake by baclofen (Wojnicki, 2009, unpublished results). It may be possible then to conjecture that intake-reducing effects of baclofen can be affected by starch as well as fat.

In conclusion, the key finding of this study is that the presence of starch can affect the ability of baclofen to decrease the intake of fat emulsions. Baclofen had no effect or stimulated intake of 1%, 3.2%, 10%, and 32% concentration fat emulsions that lacked starch. The textural qualities of the fat emulsions also did not appear to influence intake since there was no consistent trend with the fat emulsions with or without the thickener. Similarly, the manipulations in the concentration of fat or the type of fat used did not show a consistent tendency in mediating baclofen's effects on intake. Research on how the reward and palatability of food modulate intake is important since their overconsumption can lead to individuals becoming overweight or obese, a risk factor for the number one killer of Americans, cardiovascular disease.

References

Ackroff, K., Lucas, F., Sclafani, A., 2005. Flavor preference conditioning as a function of fat source. Physiology and Behavior 85, 448-60.

Ackroff, K., Vigorito, M., Scalfani, A., 1990. Fat appetite in rats, the response of infant and adult rats to nutritive and non-nutritive oil emulsions. Appetite 15, 171-88.

Addae, J.I., Rothwell, N.J., Stock, M.J., Stone, T.W., 1986. Activation of thermogenesis of brown fat in rats by baclofen. Neuropharmacology 25, 627-31.

American Heart Association Statistics Committee and Stoke Statistics Subcommittee, American Heart Association. Heart Disease and Stroke Statistics-2009 Update. United States, 2009. http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA. 108.191261. (accessed 4 October 2009).

Ariwodola, O.J., Weiner J.L., 2004. Ethanol potentiation of GABAergic synaptic transmission may be self-limiting: role of presynaptic GABA(B) receptors. J Neurosci 24, 10697-86.

Avena, N.M., Rada, P., Hoebel, B.G., 2009. Sugar and fat bingeing have notable differences in addictive-like behavior. J Nut 139, 623-8.

Bassareo, V., De Luca, M.A., Di Chiara, G., 2002. Differential expression of motivational stimulus properties by dopamine in nucleus accumbens shell versus core and prefrontal cortex. J Neurosci 22, 4709-19.

Berner, L.A., Bocarsly, M.E., Hoebel, B.G., Avena, H.M., 2009. Baclofen suppresses binge eating of pure fat but not a sugar-rich or sweet-fat diet. Behav Pharmacol, Epub ahead of print.

Berthoud, H.R., 2006. Homeostatic and non-homeostatic pathways involved in the control of food intake and energy balance. Obesity 14, 197S-200S.

Billinton, A., Ige, A.O., Bolam, J.P., White, J.H., Marshall, F.H., Emson, P.C., 2001. Advances in the molecular understanding of GABA(B) receptors. Trends Neurosci 24, 277-82.

Blein, S., Hawrot, E., Barlow, P., 2000. The metabotropic GABA receptor: molecular insights and their functional consequences. Cell Mol Life Sci 57, 635-50.

Nelson D.L., Cox M.M. Lehninger Principles of Biochemistry, 2008. CITY: W.H.Freeman, pp. 343-348.

Brebner, K., Ahn, S., Phillips, A.G., 2005. Attenuation of *d*-amphetamine self-administration by baclofen in the rat. Psychopharmacology 117, 409-17.

Brebner, K., Childress, A.R., Roberts, D.C.S., 2002. A potential role for GABA-B agonists in the treatment of psychostimulant addiction. Alcohol Alcohol 37, 478-84.

Broft, A.I., Spanos, A., Corwin, R.L., Mayer, L., Steinglass, J., Devlin, M.J., Attia, E., Walsh, B.T., 2007. Baclofen for binge-eating: an open-label trial. Int J Eat Disord 40, 687-91.

Buda-Levin, A., Wojinicki, F.H.E., Corwin, R.L., 2005. Baclofen reduces fat intake under binge-type conditions. Physiology and Behavior 86, 176-84.

Conzelmann, U., Meyer, D.K., Sperk, G., 1986. Stimulation of receptors of gamma-aminobutyric acid modulates the release of cholecystokinin-like immunoreactivity from slices of rat neostriatum. Br J Pharmacol 89, 845-52.

Cooper, J.R., Bloom, F.E., Roth, R.H. The Biochemical Basis of Neuropharmacology, 2003. New York: Oxford, pp. 105-121.

Corwin, R.L., Buda-Levin, A., 2004. Behavioral models to binge-type eating. Physiology and Behavior 82, 123-30.

Corwin, R.L., Wojnicki, F.H., 2006. Binge eating in rats with limited access to vegetable shortening. Curr Protoc Neurosci 9.23B1-9.23B11.

Corwin, R.L., Wojnicki, F.H.E., 2009. Baclofen, raclopride, and naltrexone differentially affect intake of fat and sucrose under limited access conditions. Behav Pharmacol 20, 537-48.

Corwin, R.L., Wojnicki, F.H.E., Fisher, J.O., Dimitriou, S.G., Rice, H.B., Young, M.A., 1998. Limited access to a dietary fat option affects ingestive behavior but not body composition in male rats. Physiology and Behavior 65, 545-53.

Cousins, M.S., Roberts, D.C., de Wit, H., 2002. GABA(B) receptor agonists for the treatment of drug addiction: a review of recent findings. Drug Alcohol Depend 65, 209-20.

de Araujo, I.E., Rolls, E.T., 2004. Representation in the human brain of food texture and oral fat. J Neurosci 24, 3086-93.

Dewey, S.L., Chaurasia, C.S., Chen, C.E., Volkow, N.D., Clarkson, F.A., Porter, S.P., Straughter-Moore, R.M., Alexoff, D.L., Tedeschi, D., Russo, N.B., Fowler, J.S., Brodie, J.D., 1997. GABAergic attenuation of cocaine-induced dopamine release and locomotor activity. Synapse 25, 393-8.

DiCiano, P., Everitt, B.J., 2003. Differential control over drug-seeking behavior by drug-associated conditioned reinforcers and discriminative stimuli predictive of drug availability. Behav Neurosci 117, 952-60.

Dockray, G.J., 2009. Cholecystokinin and gut-brain signaling. Regul Pept 155, 6-10.

Drewnowski, A., Greenwood, M.R., 1983. Cream and sugar: human preferences for high-fat foods. Physiology and Behavior 30, 629-33.

Drewnowski, A., Shrager, E.E., Lipsky, C., Steller, E., Greenwood, M.R., 1989. Sugar and fat: sensory and hedonic evaluation of liquid and solid foods. Physiology and Behavior 45, 177-83.

Ebenezer, I.S., 1995. Intraperitoneal administration of baclofen increases consumption of both solid and liquid diets in rats. Euro J Pharamacol 273, 183-5.

Ebenezer, I.S., 1996. Baclofen pretreatment attenuates the suppressant effect of intraperitoneal administration of cholecystokinin (CCK) on food intake in rats. Brain Res Bull 41, 269-71.

Ebenezer, I.S., Baldwin, B.A., 1990. Effect of intracerebroventricular administration of the GABAB-receptor agonist baclofen on operant feeding in satiated pigs. Br J Pharamcol 101, 559-62.

Ebenezer, I.S., Patel S.M., 2004. Effects of the GABAB agonists baclofen and 3-aminopropylphosphinic acid (3-APA) on food intake in rats. Methods Find Exp Clin Pharmacol 26, 627-30.

Ebenezer, I.S., Prabhaker, M., 2007. The effects of intraperitoneal administration of the GABA(B) receptor agonist baclofen on food intake in CFLP and C57BL/6 mice. Eur J Pharmacol 569, 90-3.

Ebenezer, I.S., Pringle, A.K., 1992. The effect of systemic administration of baclofen on food intake in rats. Neuropharmacology 31, 39-42.

Echo, J.A., Lamonte, N., Ackerman, T.F., Bodnar R.J., 2002. Alterations in food intake elicited by GABA and opiod agonists and antagonists administered into the ventral tegmental region of rats. Physiology and Behavior 76, 107-16.

Elizalde, G., Sclafani, A., 1990. Fat appetite in rats: flavor preferences conditioned by nutritive and non-nutritive oil emulsions. Appetite 15, 189-97.

Farah H., Buzby, J. U.S. Food Consumption Up 16 Percent Since 1970. November 2005. Internet: http://www.ers.usda.gov/AmberWaves/November05/Findings/

USFoodConsumption.htm (accessed 4 October 2009).

Ferssiwi, A., Cardo, B., Velley, L., 1987. Gustatory preference-aversion thresholds are increased by ibotenic acid lesion of the lateral hypothalamus in the rat. Brain Research 437, 142-50.

Foltin, R.W., 2005. Baclofen decreases feeding in non-human primates. Pharmacol Biochem Behav 82, 608-14.

Food and Agriculture Organization of the United Nations, World Health Organization. Toxicological Evaluation of Some Extraction Solvents and Certain Other Substances. Switzerland, 1970. http://www.inchem.org/documents/jecfa/jecmono/v48aje08.htm. (accessed 29 Nov 2009).

Fukuwatari, T., Shibata, K., Iguchi, K., Saeki, T., Iwata, A., Tani, K., Sugimoto, E., Fushiki, T., 2003. Role of gestation in the recognition of oleate and triolein in anosmic rats. Physiology and Behavior 78, 579-83.

Gaillard, D., Passilly-Degrace, P., Besnard, P., 2008. Molecular mechanisms of fat preference and overeating. New York Academy of Sciences 1141, 163-75.

Goto, Y., Tache, Y., Debas, H., Novin, D., 1985. Gastric acid and vagus nerve response to GABA agonist baclofen. Life Sci 36, 2471-5.

Higgs, S., Barber, D.J., 2004. Effects of baclofen on feeding behavior examined in the runway. Prog Neuropsychopharamcol Biol Psychiatry 28, 405-8.

Hopman, W.P., Jansen, J.B., Lamers, C.B., 1985. Comparative study of the effects of equal amounts of fat, protein, and starch on plasma cholecystokinin in man. Scand J Gastroenterol 20, 843-7.

Horton, R.W., LeFeuvre R.A., Rothwell, N.J., Stock, M.J., 1988. Opposing effects of activation of Central $GABA_A$ and $GABA_B$ receptors on brown fat thermogenesis in the rat. Neuropharmacology 27, 363-6.

Kinney, N.E., Antill, R.W., 1996. Role of olfaction in the formation of preference for high-fat foods in mice. Physiology and Behavior 59, 475-8.

Klitenick, M.A., DeWitte, P., Kalivas, P.W., 1992. Regulation of somatodendritic dopamine release in the ventral tegmental area by opiods and GABA: an in vivo microdialysis study. J Neurosci 12, 2623-32.

Laugerette, F., Passilly-Degrace, P., Patris, B., Niot, I., Febbraio, M., Montmayeur, J., Besnard, P., 2005. CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. The J of Clinical Investigation 115, 3177-84.

Lee, A.K., Mojtahed-Jaberi, M., Kyriakou, T., Aldecoa-Otalora Astarloa, E., Arno, M., Marshall, N.J., Brain, S.D., O'Dell, S.D., 2009. Effect of high-fat feeding on expression of genes controlling availability of dopamine in mouse hypothalamus. Nutrition, Epub ahead of print.

Lewis, L.D., Williams, J.A., 1990. Regulation of cholecystokinin secretion by food, hormones, and neural pathways in the rat. Am J Physiol 258, 512-8.

Liang, N., Hajnal, A., Norgren, R., 2006. Sham feeding corn oil increases accumbens dopamine in the rat. Am J Physiol Regul Inrtegr Comp Physiol 291, 1236-39.

Lowe, M.R., Levine, A.S., 2005. Eating Motives and the Controversy over Dieting: Eating less than needed versus less than wanted. Obesity Research 13, 797-806.

Lucas, F., Ackroff, K., Sclafani, A., 1989. Dietary fat-induced hyperphagia as a function of fat type and physical form. Physiology and Behavior 45, 937-46.

Lutter, M., Nestler, E.J., 2009. Homeostatic and hedonic signals interact in the regulation of food intake. J Nutr 139, 629-32.

Mela, D.J., 1988. Sensory assessment of fat content in fluid dairy products. Appetite 10, 37-44.

Mela, D.J., Langley, K.R., Martin, A., 1994. Sensory assessment of fat content: effect of emulsion and subject characteristics. Appetite 22. 67-81..

Mindell, S., Smith, G.P., Greenberg, D., 1990. Corn oil and mineral oil stimulate sham feeding in rats. Physiology and Behavior 48, 283-7.

National Center for Health Statistics, World Health Organization. Prevalence of overweight, obesity and extreme obesity among adults: United States, trends 1976-80 though 2005-2006. United States, 2008. https://apps.who.int/infobase/reportviewer.aspx?rptcode=ALL&uncode=840&dm=5&surveycode=102913a1. (accessed 4 October 2009).

Partosoedarso, E.R., Young, R.L., Blackshaw, L.A., 2001. GABA(B) receptors on vagal afferent pathways: peripheral and central inhibition. Am J Physiol Gastrointest Liver Physiol 280, 658-68.

Patel, S.M., Ebenezer, I.S., 2008a. The effects of acute multiple intraperitoneal injections of the GABAB receptor agonist baclofen on food intake in rats. Eur J Pharmacol 601, 106-10.

Patel, S.M., Ebenezer, I.S., 2008b. The effects of chronic intraperitoneal administration of the GABAB receptor agonist baclofen on food intake in rats. Euro J Pharmacol 593, 68-72.

Paterson, N.E., Froestl, W., Markou, A., 2004. The GABAB receptor agonists baclofen and CGP44532 decreased nicotine self-administration in the rat. Psychopharmacology (Berl) 172, 179-86.

Ramirez, I., 1991a. Chemoreception for an insoluble nonvolatile substance: starch taste? Am J Physiol 260, 192-9.

Ramirez, I., 1991b. Thresholds for starch and polycose are lower than for sucrose in rats. Physiol Behav 50, 699-703.

Ramirez, I., 1992. Chemoreception for fat: do rats sense triglycerides directly? Appetite 18, 193-206.

Ramirez, I., 1993a. Rats discriminate between starch and other substances having a similar texture. Physiol Behav 53, 373-7.

Ramirez, I., 1993b. Relative preference for starch and sugar in rats. Physiol Behav 54, 1195-1200.

Ramirez, I., 1993c. Role of olfaction in starch and oil preference. Am J Physiology 265, 1404-9.

Ranaldi, R., Poeggel, K., 2002. Baclofen decreases methamphetamine self-administration in rats. Neuroreport 13, 1107-10.

Rao, R.E., Wojnicki, F.H.E., Coupland, J., Ghosh, S., Corwin, R.L., 2008. Baclofen, raclopride and naltrexone differentially reduce solid fat emulsion intake under limited access conditions. Pharmacol Biochem Behav 89, 581-90.

Raiteri, M., Bonanno, G., Paudice, P., Cavazzani, P., Schmid, G., 1996. Human brain cholecystokinin: release of cholecystokinin-like immunoreactivity (CCK-LI) from isolated cortical nerve endings and its modulation though GABA(B) receptors. J Pharmacol Exp Ther 278, 747-51.

Rice, H.B., Greenberg, D., Corwin, R.L., 2000. Different preferences for oils with similar fatty acid profiles. Physiology and Behavior 68, 755-59.

Roberts, D.C., 2005. Preclinical evidence for GABA-B agonists as a pharmacotherapy for cocaine addiction. Physiol Behav 86, 18-20.

Sadiq, S.A., Poopatana, C.A., 2007. Intrathecal baclofen and morphine in multiple sclerosis patients with severe pain and spasticity. J Neurol 254, 1464-65.

Santiago, M., Machado, A., Cano, J., 1993. In vivo release of dopamine from rat striatum, substantia nigra and prefrontal cortex: differential modulation by baclofen. British J Pharmacol 109, 814-18.

Santiago, M., Machado, A., Cano, J., 1993. Regulation of the prefrontal cortical dopamine release by GABAA and GABAB receptor agonists and antagonists. Brain Research 630, 28-31.

Sato, I., Arima, H., Ozaki, N., Watanabe, M., Goto, M., Shimizu, H., Hayashi, M., Banno, R., Nagasaki, H., Oiso, Y., 2007. Peripherally administered baclofen reduced food intake and body weight in db/db as well as diet-induced obese mice. FEBS Lett 581, 4857-64.

Sawano, S., Takeda, M., Imaizumi, M., Manabe, Y., Kuroda, K., Fushiki, T., 2000. Biochemical studies of dopaminergic activation by stimuli of corn oil in the oral cavity of mice. Methods Find Exp Clinical Pharmacol 22, 223-27.

Sclafani, A., 2004a. Oral and postoral determinants of food reward. Physiology and Behavior 81, 773-79.

Sclafani, A., 2004b. The sixth taste? Appetite 42, 1-3.

Sclafani, A., Azzara, A.V., Touzani, K., Grigson, P.S., Norgren, R., 2001. Parabrachial nucleus lesions block taste and attenuate flavor preference and aversion conditioning in rats. Behav Neurosci 115, 920-33.

Sclafani, A., Nissenbaum, J.W., Vigorito, M., 1987. Starch preference in rats. Neurosci Biobehav Rev 11, 253-62.

Sclafani, K., Ackroff, K., Abumrad, N.A., 2007. CD36 gene deletion reduces fat preference and intake but not post-oral fat conditioning in mice. Am J Physiol Regulatory Integrative Comp Physiol 293, 1823-32.

Smith, B.R., Boyle, A.E., Amit, Z., 1999. The effects of GABA(B) agonist baclofen on the temporal and structural characteristics of ethanol intake. Alcohol 17, 231-40.

Smith, G.P., Greenberg, D., 1991. Orosensory stimulation of feeding by oils in preweanling and adult rats. Brain Res Bull 27, 379-82.

Sobik, L., Hutchinson, K., Craighead, L., 2005. Cue-elicited craving for food: a fresh approach to the study of binge eating. Appetite 44, 253-61.

Stromberg, M.F., 2004. The effect of baclofen alone and in combination with naltrexone on ethanol consumption in the rat. Pharmacol Biochem Behav 78, 743-50.

Takeda, M., Sawano, S., Imaizumi, M. Fushiki, T., 2001. Preference for corn oil in olfactory-blocked mice in the conditioned place preference test and the two-bottle choice test. Life Sciences 69, 847-54.

Touzani, K. Sclafani, A., 2001. Conditioned flavor preference and aversion: role of the lateral hypothalamus. Behav Neurosci 115, 84-93.

Verhagen, J.V., Kadohisa, M., Rolls, E.T., 2004. Primate insular, opercular taste cortex: neuronal representations of the viscosity, fat texture, grittiness, temperature, and taste of foods. J Nuerophysiol 92, 1685-99.

Verhagen, J.V., Rolls, E. T., Kadohisa, M., 2003. Neurons in the primate orbitofrontal cortex respond to fat texture independently of viscosity. J Neurophysiol 90, 1514-25.

Ward, B.O. Somerville, E.M., Clifton, P.G., Intraaccumbens baclofen selectively enhances feeding behavior in the rat. Physiology and Behavior 68, 463-8..

Weatherford, S.C., Greenberg, D., Gibbs, J., Smith, G.P., 1990. The potency of D-1 and D-2 receptor antagonists is inversely related to the reward value of sham-fed corn oil and sucrose in rats. Pharmacol Biochem Behav 37, 317-23

Wells, A.S., Read, N.W., Uynas-Moberg, K., Alster, P., 1997. Influences of fat and carbohydrate on postprandial sleepiness, mood, and hormones. Physiol Behav 61, 679-86.

Wojnicki, F.H.E., Roberts, D.C., Corwin, R.L., 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.

Xi, Z.X., Stein E.A., 1999. Baclofen inhibits heroin self-administration behavior and mesolimbic dopamine release. J Pharmacol Exp Ther 290, 1369-74.

Yomiya, K., Matsuo, N., Tomiyasu, S., Yoshimoto, T., Tamaki, T., Suzuki, T., Matoba, M., 2009. Baclofen as an adjuvant analgesic for cancer pain. Am J Hosp Palliat Care 26, 112-8.

Zarrindast, M.R., Hosseini-Nia, T., Allah-Maddadi, S., 1989. Food intake suppressant effect of baclofen in rats. Gen Pharmacol 20, 701-3.

Schreyer Honors College

Academic Vita of Danielle C. Wilt

Danielle C. Wilt
3910 Ash Drive
Allison Park, PA
15101
E-mail Id: dcw5017

EDUCATION:

Major: Science

Minor: Psychology

Honors: Nutritional Sciences

THESIS:

Thesis Title: Intraperitoneal Administration of Baclofen Fails to Reduce Intake of Fat Emulsions Lacking Starch in Rats

Thesis Supervisor: Rebecca L. Corwin

WORK EXPERIENCE:

Accessible Dental Services, Inc Internship *Pittsburgh, PA, Summer 2009*

Company provided access to dental care for those with intellectual and developmental disabilities. Assisted with clinical work and associated paperwork and billing.

Pittsburgh Tissue Engineering Initiative Research Internship *Pittsburgh, PA, Summer 2008*

Performed research in conjunction with University of Pittsburgh Medical Center's Department of Orthopedic Surgery. Created and presented formal scientific poster and abstract on personal research endeavors. Research focused upon strength of various meniscal root suture techniques.

Runners Cleaners	Clerk	*Allison Park, PA, 2003-2008*
Atria's Restaurant	Waitress	*Wexford, PA, 2005-2007*
Max & Erma's Restaurant	Hostess	*Gibsonia, PA, 2004-2005*

ACTIVITIES:

Volunteer at State College Presbyterian Church	*2008-2009*
PSU Pre-Dental Society	*2007-2009*
PSU Rugby Football Club	*2006-2007*

AWARDS:

Academic Excellence Award	*2006-2009*
Dean’s List	*2006-2009*