The Effect of Acute and Chronic High Fructose Corn Syrup Pre-exposure on Naltrexone-Induced Conditioned Place Aversion

By

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ABSTRACT

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Withdrawal is a major component of addiction. Antagonism of mu-opioid receptors (MOR) results in withdrawal following ingestion of sugars and drugs of abuse. We hypothesize that naltrexone (NTX) will precipitate affective withdrawal following ingestion of HFCS. Affective withdrawal was assessed using conditioned place avoidance (CPA). Food restriction was employed to investigate the effects of increased HFCS consumption. In a separate experiment intragastric infusions of HFCS will be given prior to NTX conditioning. Effects will be compared with CPA after acute and chronic heroin. NTX-induced a CPA in naïve animals regardless of HFCS exposure. Increased HFCS consumption resulted in NTX-induced CPA with both intragastric administration and food restriction, not seen with 0% HFCS. A significant CPA was observed after acute and chronic heroin administration, which was greater than control animals. Therefore, NTX failed to precipitate an affective withdrawal after pre-exposure to HFCS that was comparable with heroin.
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General Introduction

Over-consumption of highly palatable foods poses a major threat to global health and wellbeing. In fact, due to the alarming rise of non-communicable diseases, it is predicted that for the first time in recorded history there is going to be a decline in life expectancy (Olshansky and Passaro 2005). A major reason for this change is due to rising incidences of diabetes and cardiovascular disorders, which in part are attributed to the growing rates of obesity (McIntyre et al. 2011). The route cause of these disorders is largely associated with a number of unhealthy behaviors including: tobacco use, harmful alcohol consumption, physical inactivity and unhealthy eating habits (Alwan 2011). These behaviors generally involve the ingestion of licit substances including psychoactive drugs and highly palatable foods. While clear guidelines exist for diagnosing and treating drug dependence, less research has focused on whether excessive caloric intake shares similar criteria for addiction.

The food addiction hypothesis was first described as an inability to become sensitized to the physiological effects of food (Randolph 1956). Continued consumption of particular foods was thought to result in the development of tolerance and withdrawal similar to that of psychoactive drugs. Specifically, individuals with unhealthy eating habits were seen to increase food consumption in order to achieve the same desired effects. Furthermore, withdrawal or “hangovers” were also associated with unhealthy eating habits. Negative emotional states were observed when access to foods was restricted. These withdrawal like states were said to be alleviated by the “hair of the same dog”, wherein ingestion of only certain foods could help to reduce the negative consequences of withdrawal from that same food. However, due to the necessity of food
for survival and the wide spread acceptance of use, individuals with problematic eating habits were resistant to being identified as having a pathology. Therefore, the food addiction hypothesis was developed as a means of drawing parallels between behaviors associated with compulsive food consumption and drug use. This allowed for a greater acceptance of lingo related to unhealthy eating habits by drawing parallels with drug use (Randolph 1956).

In order to operationalize the food addiction hypothesis, the Yale Food Addiction Scale (YFAS) was developed based on criteria for substance abuse and dependence outlined in the Diagnostic Statistical Manual-IV (DSM-IV) (Gearhardt et al. 2011). This 25-item questionnaire uses dimensional and binary items to identify symptoms of unhealthy eating habits that parallel behaviors associated with psychoactive drug use (Gearhardt et al. 2012). In order to be classified as a “food addict”, individuals were required to demonstrate at least 3 of 7 symptoms for drug dependence, along with clinical impairments or distress (Pursey et al. 2014). Recently, the YFAS has been modified and adapted to meet the requirements of the DSM-V (Meule and Gearhardt 2014). Symptoms of abuse and dependence have been merged into a classification of addiction, and a new symptom of craving or a strong desire to use the substance has been added to the diagnostic criteria. Addiction severity has been included with a range from mild to severe, and two symptoms are now required instead of three for a classification of addiction (Meule and Gearhardt 2014). The ability of the YFAS to conform to these updated criteria shows that it is an adaptable measure that conforms to the current standards of addiction.
Validation of the YFAS has been assessed through a number of measures. For instance, adequate convergent validity has been found through significant correlations with food addiction and similar constructs associated with eating pathology. Furthermore, limited associations with similar but distinct impulsivity traits associated with problematic alcohol use have been distinguished from criteria for food addiction, demonstrating the discriminative validity. Finally, incremental validity was shown through the YFAS ability to identify distinct patterns of binge eating behavior, adding a separate and distinct aspect to the food addiction hypothesis beyond previously established measures (Gearhardt et al. 2013).

The YFAS has identified a number of epidemiological and population level variables indicative of food addiction. For instance, a large-scale meta-analysis determined the prevalence of food addiction to be 19.9% in sampled participants. The majority of diagnoses were made in individuals who were obese, over the age of 35 and female (Pursey et al. 2014). Scores on the YFAS were correlated with comorbid mental health problems commonly diagnosed in individuals with drug addiction including: depression, negative affect, lower self-esteem and emotional dysregulation (Gearhardt et al. 2012). A number of neurological correlates indicative of drug addiction have also been associated with the YFAS. In response to food related cues, scores on the YFAS positively correlated with hyperactivity in brain regions involved in inhibitory control, representing a greater need for self-regulation in response to food cues. This suggests that food addicts are in a constant state of self-regulation, continually battling urges to resist food consumption. In addition, decreased brain activity was found in brain regions of food addicts that are involved in the ingestion of food, and these measures correlated
significantly with scores on the YFAS (Gearhardt et al. 2011). This suggests that in addition to enhanced responsivity to food related cues; food addiction is also associated with the devaluation of rewards associated with the actual consumption of food. These symptoms are highly similar to those observed with chronic drug use, such as incentive sensitization and tolerance. Specifically, contextual stimuli associated with drug use become highly salient, while the actual reward value is greatly diminished. This results in a greater focus on obtaining the drug due to its salient properties and greater intake of the drug in order to achieve the same desired effects (Robinson and Berridge 1993; Koob et al. 1997).

While the food addiction hypothesis is gaining more traction, an inherent problem in trying to characterize food in the same category as drugs of abuse is that; unlike drugs, food is necessary for survival. However, the possibility remains that food itself is not addictive but the product of industrialized refinement that creates a highly potent, and highly rewarding substance could be addictive. Specifically, a food that is highly concentrated with fat, salt or sugar is analogous to cocaine, which is refined from the cocoa plant or heroin from poppies. As a result these artificial substances may elicit physiological responses that alter brain reward thresholds, leaving certain individuals vulnerable to developing problematic eating habits representative of addiction (Ifland et al. 2009).

An example of a highly potent food rich in concentrated sugars is high fructose corn syrup (HFCS) (Mark and White 1993). Over the last 30 years HFCS, has begun replacing sucrose in many industrial products due to the inexpensive cost of production. Soft drinks are the number one source of sugar in the average diet containing large
amounts of HFCS. Increasing consumption of soft drinks and related products have been found in children and adolescents over the last decade. This is extremely worrying because consumption of products highly concentrated with HFCS is correlated with increases in weight gain and obesity (Brown et al. 2008).

A number of neurological changes have been observed following chronic HFCS intake that may contribute to the development of addictive behavior. For instance, rats given a liquid fructose solution for four weeks showed a 40% reduction of Brdu immunoreactive cells in the hippocampus indicating deficits in neurogenesis (van der Borght et al. 2011). Furthermore, rats given two and a half weeks of access to a high fructose diet showed increased latencies to find platforms in the Morris water maze. This suggests deficits in spatial memory or a decreased motivation to alleviate aversive states after chronic sugar consumption (Ross et al. 2009). Reductions in hippocampal volume and associated cognitive deficits related to memory functioning and motivation are also thought to be key factors involved in the development and maintenance of drug addiction (Eisch and Harburg 2006). Therefore, chronic sugar consumption alters neurobehavioral functioning in brain regions involved in addiction.

Sugar is a highly rewarding substance that activates both dopaminergic and opioidergic systems in reward related brain regions (Drewnowski et al. 1995; Hajnal and Norgren 2001). Opiate agonists and many drugs of abuse mimic these endogenous neurotransmitters (Koob and Volkow 2010). Injections of mu-opioid agonists into the rostral dorsal region of the nucleus accumbens increases sucrose intake and orofacial reactions to a sweet solution (Castro and Berridge 2014). In addition, both sugar and drug intake are decreased by antagonism of mu-opioid (MOR) and D1 receptors (Carati and
Schenk 2011; Jones et al. 2011; Buck et al. 2014). High densities of MOR in the rostral dorsal region of the nucleus accumbens termed the “hedonic hotspot” implicate opioidergic functioning in reward processing of both sugars and drugs of abuse. Opiate agonists such as heroin and morphine are used recreationally and habitually due to their euphoric effects, which largely occur through activation of MOR and D-1 receptors (Koob and Volkow 2010; Lutz and Kieffer 2013). Therefore, sugar and drugs of abuse share similar neurological pathways to establish their hedonic values, which indicates that disruption of these pathways may contribute to similar addictive processes.

The cycle of drug addiction involves both positive and negative reinforcement. Initial drug use is driven by the rewarding properties of drugs, while later intake is focused on alleviating negative affective states associated with withdrawal (Koob et al. 1997). A number of physiological indices of withdrawal have also been observed following cessation of intermittent sugar access. Animals given cyclic access to a 25% sugar solution demonstrated a significant decrease in body temperature and increases in anxiety and aggressive behaviors when sugar is removed from their diets. This effect lasts for an entire week after sugar has been removed. Even more interestingly body temperature was restored and anxiety and aggressive like behaviors attenuated following reintroduction of the sugar solution (Wideman et al. 2005). These findings indicate that sugar can induce a spontaneous withdrawal state.

Furthermore, evidence suggests that withdrawal from sugars can also be precipitated with a mu-opioid receptor (MOR) antagonist. For instance, animals given cyclic access to glucose and rat chow show somatic signs of withdrawal when administered the non-selective MOR antagonist naloxone. Physical signs of withdrawal
include: teeth chattering, forepaw tremor and headshakes. In addition, lower doses of naloxone also increased anxiety like behavior in an elevated plus maze. These behavioral markers of withdrawal were also associated with neurological changes seen with drug dependence, including decreases in D-1 receptors and increased acetylcholine within the nucleus accumbens (Colantuoni et al. 2002).

While physical indices of withdrawal are integral to drug addiction, the motivational components are generally described as the most detrimental aspects (Koob et al. 1997). Negative aversive states including anhedonia and depressed moods last long after substance use has ceased leaving individuals vulnerable to relapse even when somatic signs have subsided (Sakoori and Murphy 2005). While a number of physical and behavioral measures of sugar withdrawal have been characterized, no study has investigated the affective component.

In animal research it is difficult to ascertain higher order motivational states due to lack of verbal communicative abilities. However, using the principles of classical conditioning, motivation is determined through avoidance or approach of stimuli previously paired with rewarding or aversive states. Using the procedure of conditioned place avoidance (CPA), the affective consequences of morphine withdrawal have been well validated in animal literature (Azar et al. 2003). Animals exposed to acute or chronic morphine, show significantly greater avoidance of compartments paired with a MOR antagonist compared to control animals. Thus, the CPA procedure measures the motivation of animals to avoid withdrawal-paired stimuli.

The present study investigates the motivational component of sugar withdrawal. Due to the well-documented nature of motivational withdrawal from drugs of abuse we
hypothesize that rats given acute and chronic HFCS pre-exposure will show similar withdrawal like behaviors. Furthermore, we expect that chronic consumption of HFCS will result in increased measures of withdrawal compared with acute ingestion. The non-selective mu-opioid receptor antagonist naltrexone will be used to precipitate this negative motivational state. Manipulation of the amount of HFCS consumed will be conducted in order to measure the pharmacological properties of this effect. Furthermore, acute and chronic heroin will be administered as a means of comparing naltrexone-precipitated affective withdrawal after pre-exposure to sugar and drugs.
Alterations of naltrexone-induced place avoidance by pre-exposure to high fructose corn syrup or heroin in Sprague-Dawley rats

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Abstract

Rationale: The affective component of withdrawal is a core feature of drug addiction. It has been suggested that withdrawal from sugars produces a set of somatic symptoms that resemble those observed following withdrawal from opiate drugs. Objectives: The current study explored whether acute or chronic pre-exposure to a sugar solution alters a negative affective state precipitated by naltrexone. To interpret the findings, the experiments were repeated in rats pre-exposed to acute or chronic heroin. Methods: Male Sprague-Dawley rats: received intragastric acute administration of high fructose corn syrup (HFCS; 0.5, 1 or 2 g/kg); drank 0% or 50% solutions of HFCS in their home cages for 22 days; received acute subcutaneous (SC) injections 2 mg/kg heroin; or were implanted (SC) with osmotic mini-pumps releasing 3.5 mg/kg/day heroin. Following these pre-treatments, animals were tested on place conditioning induced by naltrexone (1 or 3 mg/kg, SC). Results: Both doses of naltrexone produced a conditioned place avoidance in naive rats. Importantly, neither acute nor chronic HFCS pre-exposure significantly amplified this effect, but both acute and chronic heroin pre-exposure did. Conclusions: These results in rats fail to support the hypothesis that an opioid antagonist can precipitate similar affective withdrawal states following pre-exposure to sugars and opiates.

Keywords
Introduction

The food addiction hypothesis suggests that compulsive eating habits can resemble behaviors associated with pathological drug use (Randolph 1956; Meule and Gearhardt 2014). This has been explained by common actions of highly palatable foods and drugs of abuse on neurochemical systems that regulate learning and motivational processes (Ifland et al. 2009; Kenny 2013). Furthermore, the diagnostic criteria for substance dependence have been adapted to describe addictive patterns of food consumption that lead to negative social and health consequences (Ziauddeen et al. 2012; Meule and Gearhardt 2014).

Withdrawal can be considered a central feature of drug dependence. Although the cluster of symptoms experienced differ between drugs, withdrawal is typically described as an aversive physiological and psychological state which occurs during cessation of drug use, or which can be “precipitated” pharmacologically. For example, in individuals dependent on opiates, the administration of competitive antagonists such as naloxone or naltrexone rapidly precipitates a variety of symptoms that include: pupillary dilation, nausea, diarrhea and restlessness (Ali et al. 2003). Both somatic and psychological components of opiate withdrawal can be precipitated with a mu-opioid receptor antagonist in multiple species (Williams et al. 1976; Mucha et al. 1982; Wright et al. 1991). Withdrawal symptoms are broadly classified in two categories. Non-purposive symptoms, occur independently of drug seeking behavior, described as somatic or
physical signs including: a decreased respiratory rate, lowered blood pressure, pupillary dilation, drowsiness, vomiting and diarrhea (Blachly 1966). Purposive symptoms reflect psychological manifestations of anhedonia and depressive moods, which can result in renewed drug use as a means of self-medication (Cook et al. 2010). This psychological component can last for months after cessation of drug use and is generally described as the most difficult aspect of protracted abstinence (Koob and Moal 1997).

Is there evidence of withdrawal signs in the context of food addiction? In laboratory animals, there is indeed evidence of somatic withdrawal following binge patterns of sugar intake (Colantuoni et al. 2002). That is, animals given intermittent access to sugar display opioid-like withdrawal signs such as decreases in body temperature and increased aggressive and anxiety like behavior (Wideman et al. 2005). Interestingly, the administration of naloxone in sugar binging rats has also been reported to increase anxiety-like behavior and produce neurochemical alterations in the ventral striatum (Colantuoni et al. 2002).

The current study was performed to investigate whether an opioid receptor antagonist can precipitate a negative affective state in rats pre-exposed to sugar as it does in animals that have been pre-exposed to opiates. That is, rats that are injected with morphine, and soon after receive injections of naloxone/naltrexone in a specific environment, display an avoidance of that environment when tested drug-free (i.e., conditioned place avoidance; CPA). Similarly, the food addiction hypothesis would predict that rats pre-exposed to a sugar solution should display avoidance of an environment paired with injections of opioid antagonists. High fructose corn syrup (HFCS) was used in this study because of hypothesized links with obesity and other
metabolic disorders (Brown et al. 2008; Walker et al. 2014; Brisbois et al. 2014). In addition, experiments were repeated in heroin pre-exposed animals in order to evaluate the magnitude of anticipated aversions generated by HFCS pre-exposure.

Methods

Subjects

A total of 156 male Sprague-Dawley rats (Charles River, Quebec, Canada) were used as subjects. Animals were individually housed, weighing 175-200 grams at the beginning of the experiment. Upon arrival, rats were given one week of acclimatization to the facility. They were maintained on a 12-hour reverse light dark schedule (lights on 7:00 AM, off 7:00 PM), and all behavioral testing was conducted during the dark period. Water and rat chow (Purina rat chow 18% protein) were available ad-libitum throughout the experiments, unless otherwise specified. All experiments were approved by the Animal Care Committee of the University of Guelph, and were carried out in accordance with the recommendations of the Canadian Council on Animal Care.

Apparatus

HFCS administration in home cages

No-drip water bottles (Thermo Scientific) with rubber stoppers (Fisher Scientific) and metal spouts (Ancare) were used to deliver HFCS or control (water) solutions. These bottles were always in the rat’s home cages (i.e., unlimited access). Consumption of HFCS was measured daily by weighing the bottles (1.18 ml/gram). Water and food intake were also measured daily by weight consumed, and care was taken to collect any food on the floor of the cage.
Place conditioning

Six semitransparent Plexiglass chambers (University of Guelph, ON, Canada) were used for place conditioning as described previously (Sticht et al. 2010); briefly, two equally sized compartments (30 X 40 X 26 cm) separated each chamber with a removable insert (dark gray PVC). A small square opening (10 X 10 cm) at the back of each insert allowed access during pre-conditioning and test sessions, while an identical insert without an opening was used for conditioning. Distinct visual (marbled white and black pattern on the wall of one compartment and vertical white and black stripes on the wall of the other; objects external to the boxes including cabinets, tables and computer) and tactile (one compartment in each chamber contained a black ceramic floor tile) cues were maintained constant throughout the experiment. Black wire mesh covered the front of each compartment allowing for automatic video tracking (EthoVision v3, Noldus, The Netherlands). A virtual transition zone (approximately the size of a 400 gram rat) was created using this software when inserts were open, allowing for statistical independence of measures between the two compartments.

Surgery

Chronic heroin was administered by implanting osmotic mini-pumps subcutaneously (Alzet model 2ML2, 0.5 l/h for 14 days, Durect Corporation, Cupertino, CA, USA). Rats were anaesthetized with isoflurane (Pharmaceutical Partners of Canada Inc., Richmond Hill, ON, Canada), small incisions were made in the skin between the scapulae, spreading apart subcutaneous connective tissues to create a small pocket for the pumps. Osmotic mini-pumps were inserted with flow moderators directed away from the
incision. Wound clips closed incisions. Control animals received the same surgical procedures except no drug was administered through osmotic mini-pumps.

**Procedures**

Experiment 1: Naltrexone-induced CPA during chronic HFCS exposure

Control (0% HFCS; n=20) and HFCS (50% HFCS; n=20) rats were given unrestricted access to food, water and HFCS at all times, except when in the place conditioning apparatus. CPA testing began after 22 days of HFCS exposure; that is, after stabilization of HFCS drinking.

A biased procedure was used because rats generally display a preference for one compartment over the other during pre-conditioning sessions. Thus, assigning the drug-paired compartment eliminates initial biases that may affect the conditioning procedure, without the need to exclude animals from the experiment. Rats were first habituated to the conditioning apparatus for 20 minutes. Pre-conditioning began at 2:00 PM. The naltrexone-paired compartment was selected when the rat spent more time in that compartment by at least one second. This criterion for selecting the preferred compartment was used because if the animal showed a strong preference for one compartment over the other then naltrexone would reduce this bias, however if there were no preference then the design would be similar to that of an unbiased procedure. Regression to the mean was determined not to be a limiting factor because rats without naltrexone exposure did not show a significant difference in time spent in the preferred compartment from pre-conditioning to test sessions. Beginning at 2:00 PM of the following day, half of rats in each group were injected with vehicle and confined in the non-preferred compartment for 30 min. The other half were injected with 1 or 3 mg/kg
naltrexone and confined in the preferred compartment for 30 min. This was repeated three additional times (i.e., 4 vehicle and 4 naltrexone pairings in total, over 8 days). Therefore, this experiment included 4 groups (n=10 each): 0% HFCS in home cage conditioned with 1 or 3 mg/kg naltrexone, and 50% HFCS in home cage conditioned with 1 or 3 mg/kg naltrexone. Beginning at 2:00 PM following the last day of conditioning, all rats were tested for place avoidance during a 20 min test. The difference in time spent in the naltrexone-paired compartment from pre-conditioning to test was used as an index of place avoidance. Groups conditioned with 0 mg/kg naltrexone were not included because a pilot experiment indicated that four confined exposures and saline injections in each compartment of the place conditioning apparatus does not significantly alter initial compartment biases (Mean ± sem: Pre-conditioning = 646.8 ± 10.5; Test = 639.1 ± 23.9). Therefore, it is unlikely that a regression towards the mean can account for reductions in time spent in the preferred compartment from pre-conditioning to test sessions, as these animals were tested under the same conditions as experiments administering naltrexone. Furthermore, it is unlikely that chronic HFCS access would be change this because it would be available prior to as well as during conditioning sessions with both naltrexone and saline.

Experiment 2: Naltrexone-induced CPA during chronic HFCS exposure in food-restricted rats

This experiment was performed like Experiment 1, but with two critical differences. First, all rats (n=22) were food restricted and maintained at approximately 85-90% of the weight of free-fed rats during the entire duration of the experiment. Food
restriction was introduced to increase the total amount of HFCS consumed in the home cages. Second, only the highest dose of naltrexone (i.e., 3 mg/kg) was tested.

Experiment 3: Naltrexone-induced CPA after acute HFCS exposure

This experiment was performed like Experiment 1, but with four critical differences. First, in their home cages, there were no bottles of HFCS. Second, all rats (n=40) received intragastric gavages (1 ml/100 g) with water (4 infusions over 4 days) to adapt to the procedure. Third, after this period, CPA testing was performed as described above, but 0 (n=10), 0.5 (n=10), 1 (n=10) or 2 (n=7; 3 rats removed because of adverse reactions to the gavage procedure) g/kg HFCS solutions were administered by intragastric gavage 30 minutes prior to naltrexone conditioning sessions and water 30 minutes prior to saline. This time period was selected to coincide with the peak of the glucose response in blood (data not shown). Fourth, only 1 mg/kg naltrexone was used because this dose has been used to precipitate acute morphine withdrawal (Parker and Joshi 1998).

Experiment 4: Naltrexone-induced CPA during chronic heroin exposure

This experiment was performed like Experiment 1, but with four critical differences. First, in their home cages, there were no bottles of HFCS. Second, to build up tolerance prior to the implantation of the mini-pumps, rats received an injection of 1 mg/kg heroin, and 6 hours later an injection of 2 mg/kg. The following day, the same schedule was used to administer 2 and 4 mg/kg.

Third, the day following the last injection, all rats were surgically implanted with osmotic mini-pumps releasing 0 (n=12) or 3.5 (n=11; one animal was removed due to an adverse reaction to heroin) mg/kg/day heroin for 14 days. The CPA experiment began 2 days
after surgery, and it was completed within the period of chronic heroin exposure. Fourth, only 1 mg/kg naltrexone was used.

Experiment 5: Naltrexone-induced CPA after acute heroin exposure

This experiment was performed as in Experiment 1 but with three critical differences. First, rats were not exposed to HFCS in their home cages. Second, 0 or 2 mg/kg heroin was administered 24 hours prior to naltrexone conditioning sessions, and 0 mg/kg heroin was administered 24 hours prior to saline conditioning sessions. Third, only 1 mg/kg naltrexone was used.

Drugs and HFCS solutions

Naltrexone-hydrochloride (Sigma Aldrich) and diacetylemophine hydrochloride (heroin, MacFarlan Smith Ltd., Edinburgh, UK) were dissolved in saline and injected subcutaneously (SC) at a volume of 1 ml/kg. Liquid 55 HFCS (Nature’s Flavor, Orange, CA) was prepared in a 50% solution with deionized water. This concentration was selected because rats readily consume it, and display stable intake after approximately 14 days. Intragastric infusions of HFCS were administered at 1 ml/100g volume, with the highest 2 g/kg dose chosen on estimated average hourly intake. The highest dose of naltrexone (3 mg/kg) was selected because it was found to precipitate an anxiety-like state in animals’ bingeing on sucrose solutions (Colantuoni et al. 2002). Chronic heroin was administered at 3.5 mg/kg/day because of its ability to elicit spontaneous withdrawal upon termination of treatment (Leri et al. 2003). Using a 1/10 conversion ratio from morphine to heroin (Lu et al. 2002), heroin was injected at 2 mg/kg because 20 mg/kg morphine pre-treatment significantly potentiates naloxone-induced CPA (Parker and Joshi 1998).
**Statistical analyses**

Time spent in drug-paired (naltrexone) compartments on pre-conditioning and test sessions in different groups was compared by mixed-design Analyses of Variance (ANOVA). In case of significant main effects or interactions, individual mean differences were identified by multiple comparisons using the Student-Newman-Keuls method ($\alpha = 0.05$). To test specific predictions, planned comparisons between means of interests were performed using t-tests. The details of non-significant statistics are not reported. All analyses were performed using SigmaStat (v. 3.5 for Windows, SPSS Inc).

**Results**

*Experiment 1: Naltrexone-induced CPA during HFCS exposure*

Figure 1 represents time spent in the naltrexone-paired compartment during the pre-conditioning and test sessions in rats given access to 0% or 50% HFCS solutions. The ANOVA only revealed a significant main effect of Test [$F(1,36) = 49.37, p < 0.01$]. Planned comparisons further identified significant differences in time spent in the naltrexone-paired compartments from pre-conditioning to test in both 0% and 50% HFCS groups, conditioned with 1 or 3 mg/kg naltrexone [$t(9) = 3.44, p < 0.01$; $t(9) = 3.05, p < 0.05$; $t(9) = 7.31, p < 0.001$; and $t(9) = 2.94, p < 0.05$, respectively]. Therefore, there was a similar avoidance of the naltrexone-paired compartment regardless of HFCS exposure. This is unlikely to be a regression towards the mean because rats given 0 mg/kg naltrexone (methods) did not show a change in the time spent in their preferred compartment from pre-conditioning to test sessions.
Experiment 2: Naltrexone-induced CPA during HFCS exposure in food-restricted rats

Table 1 represents total consumption of rat chow and HFCS in non-food restricted (Experiment 1) and food-restricted (Experiment 2) rats. Student’s t-tests indicated a significant difference in both rat chow \([t(28) = 12.05, p < 0.001]\) and HFCS \([t(28) = 4.42, p < 0.001]\) consumption. Hence, food restriction significantly elevated consumption of HFCS.

Figure 2 represents time spent in the naltrexone-paired compartment during pre-conditioning and test sessions in food restricted rats given access to 0% or 50% HFCS solutions. The ANOVA revealed significant main effects of Group \([F(1, 20)= 5.44, p < 0.05]\) and Test \([F(1, 20)= 6.89, p < 0.05]\). Multiple comparisons further revealed a significant reduction in time spent in naltrexone-paired compartments from pre-conditioning to test only in the group exposed to 50% HFCS \((p < 0.05)\). Therefore, naltrexone-induced a CPA in animals pre-exposed to 50% HFCS and this effect was not seen in food restricted rats given 0% HFCS. However, the difference in time spent in the naltrexone-paired compartments during the test session was not significantly different between rats given 0% and 50% HFCS solutions.

Experiment 3: Naltrexone-induced CPA after acute HFCS exposure

Figure 3 represents time spent in the naltrexone-paired compartment during pre-conditioning and test sessions in animals given intragastric infusions of HFCS prior to naltrexone \((1 \text{ mg/kg})\) conditioning. The ANOVA revealed only a significant main effect of Test \([F(1, 33)=14.39, p < 0.001]\). Planned comparisons indicated there was a significant reduction in time spent in the naltrexone-paired compartment only in the groups that were administered 1 and 2 g/kg HFCS \([t(9) = 2.8, p < 0.05; t(6) = 4.78, p <\)
0.01, respectively]. Therefore, naltrexone-induced a CPA only after pre-exposure to higher doses of HFCS but, this was not seen in animals infused with 0 and 0.5 g/kg HFCS. This was similar to what was found in Experiment 2 and again, time spent in the naltrexone-paired compartment was not significantly different in rats given 1 and 2 g/kg compared to 0 g/kg HFCS.

Experiment 4: Naltrexone-induced CPA during chronic heroin exposure

Figure 4 represents time spent in the naltrexone-paired compartment during pre-conditioning and test sessions in animals given chronic heroin pre-exposure. The ANOVA revealed a significant interaction between Group and Test [F(1,21)= 8.25, p < 0.01], as well as significant main effects of Group [F(1,21)= 8.64, p < 0.01] and Test [F(1, 21)= 21.49, p < 0.001]. Multiple comparisons further highlighted significant differences in time spent in the naltrexone-paired compartment between pre-conditioning and test in heroin-treated rats (p < 0.001), and between CPA tests in rats treated with vehicle or heroin (p < 0.001). Therefore, naltrexone-induced a CPA in rats implanted with osmotic mini-pumps releasing 3.5 mg/kg/day heroin, and this effect was significantly greater than in control animals pre-treated with 0 mg/kg/day heroin.

Experiment 5: Naltrexone-induced CPA after acute heroin exposure

Figure 5 represents time spent in the naltrexone-paired compartment during pre-conditioning and test sessions in animals given acute injections of 2 mg/kg heroin 24 hours prior to naltrexone (1 mg/kg) conditioning. The ANOVA revealed a significant Group by Test interaction [F(1, 18)= 6.28, p < 0.05], as well significant main effects of Group [F(1, 18)= 10.58, p < 0.01] and Test [F(1, 18)= 49.05, p < 0.001]. Multiple comparisons further revealed a significant difference in time spent in the naltrexone-
paired compartment between animals treated with 0 and 2 mg/kg heroin (p < 0.01). A significant difference in time spent in the naltrexone-paired compartment during test sessions was also observed between animals treated with 0 and 2 mg/kg heroin (p < 0.001). Therefore, naltrexone-induced a CPA after repeated acute 2 mg/kg heroin injections that was significantly greater than in animals administered 0 mg/kg heroin.

Discussion

The affective component of withdrawal is a core feature of drug addiction. Negative emotional states remain long after substance use has ceased, leaving individuals vulnerable to relapse even when physical symptoms of withdrawal have subsided (Leventhal et al. 2009). It has been suggested that withdrawal from sugars produces a set of somatic symptoms resembling those of opiate drugs, yet whether there is also negative affective state remains unclear. Therefore, the current study determined whether 1 and 3 mg/kg naltrexone could produce conditioned place avoidance in laboratory rats receiving acute or chronic pre-exposure to high fructose corn syrup (HFCS) solutions. To interpret the findings, the same experiments were repeated in rats pre-exposed to acute or chronic heroin. It was found that both doses of naltrexone produced a CPA in naïve rats. Importantly, HFCS pre-exposure did not significantly amplify this effect beyond that seen in control animals, but heroin pre-exposure did. These results in laboratory rats fail to support the hypothesis that an opioid antagonist can precipitate similar affective withdrawal states following pre-exposure to sugars and opiates.

The basic finding of naltrexone-induced CPA is generally consistent with previous research investigating the motivational component of opioid antagonists in morphine dependent animals (Mucha 1987; Shoblock and Maidment 2006; Gómez-
Milanés et al. 2012). Naltrexone also induces a number of aversive physiological responses in non-opiate dependent human subjects including gastrointestinal discomfort, loss of energy and depressed moods (Hollister and Johnson 1981). Several reports indicate that naltrexone-induced CPA in laboratory animals reflects an avoidance of stimuli paired with its aversive effects. This is thought to result from decreased MOR activation, causing a disruption of basal hedonic tonicity maintained by opioid receptors (Narayanan et al. 2004; Cavun and Millington 2005). Furthermore, acute and chronic opiate administration potentiates naltrexone-induced aversions, creating what has been described as a withdrawal-like state in many species (Williams et al. 1976; Mucha et al. 1982; Kirby et al. 1990; Wright et al. 1991).

While naltrexone-induced a CPA in naive animals, this effect was not observed in rats that were food restricted, intragastrically infused, or exposed to surgical procedures. This is an interesting finding because others have failed to observe a CPA following conditioning with 0.1 mg/kg – 10 mg/kg naloxone (Higgins et al. 1991; Kosten 1994; Gerrits et al. 1995; Bormann, N., Cunningham 1997; Valverde and Roques 1998; Sticht et al. 2010). Perhaps, stress plays a critical role in mediating the affective properties of opioid antagonists. Food restriction raises glucocorticoid levels and related hormones (Beck and Luine 1999). As well, intragastric and surgical procedures elevate a number of physiological parameters of stress (Brown et al. 2000; Jirkof et al. 2013). It is known that endogenous opioids are also released during stress to produce compensatory inhibition of the hypothalamic-pituitary-adrenal axis (Bali et al. 2015). Therefore, stressful experimental manipulations may elevate endogenous opioid release, antagonizing naltrexone/naloxone-induced reductions in MOR tonicity. This interpretation would be
consistent with attenuated naloxone-precipitated CPA in morphine dependent animals deficient in corticotropin releasing factor receptors (Garcia-Carmona and Almela 2012).

Unexpectedly, HFCS pre-treatment did not reliably potentiate naltrexone-induced aversions to the same extent as heroin. In fact, results from Experiment 1 showed that providing animals with unlimited access to HFCS failed to alter naltrexone-induced avoidance. It was reasoned that perhaps this was due to either moderate HFCS consumption, or a lack of control over the amount of time separating HFCS ingestion and naltrexone conditioning. Therefore, two experimental manipulations were added. In Experiment 2, animals were food restricted resulting in increased HFCS consumption (see Table 1). In Experiment 3, animals were administered HFCS through intragastric gavage, allowing for investigation of naltrexone-induced CPA in animals given large amounts of HFCS just prior to conditioning.

Interestingly, HFCS pre-exposure in both these instances resulted in avoidance behavior not seen in control animals. These findings suggest that if large amounts of HFCS are ingested, naltrexone-induced CPA can be potentiated. However, statistically, the aversions to naltrexone were not different from those of the control groups. Thus, if any facilitation of the pre-treatment occurred, it was modest at best. It is unlikely that this was a byproduct of the CPA procedure employed because animals given chronic, or acute injections of heroin, displayed aversions that were large enough to be statistically different from those of control animals.

This said, there might be several reasons why HFCS pre-exposure did not potentiate naltrexone-induced CPA as predicted. First, animals had unlimited access to HFCS and rat chow in their home cages, and this differs from previous research that used
intermittent access to elicit withdrawal (Colantuoni et al. 2002; Wideman et al. 2005). Specifically, only animals given cyclic glucose and rat chow showed somatic signs of withdrawal- and anxiety-like behaviors, while animals with unlimited access did not (Colantuoni et al. 2002). The authors suggested that an increase in opioid release during cessation of sugar and food consumption promoted escalating intake in a binge-like manner, which is a core feature of the food addiction hypothesis (Avena 2010). It should be noted that, in the current study, chronic heroin pre-exposure potentiated naltrexone-induced CPA independent of an intermittent pattern of access, therefore indicating that binging is not a necessary feature of affective opiate withdrawal. Second, it is known that the reinforcing properties of HFCS and sucrose are different (Ackroff and Sclafani 2011). In the current study, HFCS was provided to animals instead of sucrose, which has been used previously to study somatic signs of sugar withdrawal (Colantuoni et al. 2002; Wideman et al. 2005). HFCS was selected because it is found in many manufactured human products, and its consumption has been correlated with increasing rates of obesity (Lakhan and Kirchgessner 2013). Third, the duration of HFCS exposure may not have been sufficiently prolonged to induce neurobiological changes related to withdrawal. For instance, a minimum of six weeks of access to a fructose solution resulted in cell loss in the nucleus solitary tract, a brain region involved in opiate withdrawal (Garcia-Carmona and Almela 2012; Rafati et al. 2013). However, the length of HFCS exposure used in this study was comparable to that of previous investigations of naloxone-precipitated somatic and neurobiological signs of sugar withdrawal with intermittent access (Colantuoni et al. 2002; Wideman et al. 2005).
In spite of these limitations, at least within the limits of experimental parameters employed in this study, it is concluded that pre-exposure to acute and chronic HFCS, unlike heroin, failed to enhance a naltrexone-induced aversive, anhedonic-like withdrawal state. These findings reveal differences in the affective component of sugar and opiate withdrawal, highlighting important distinctions in the dependence criteria for sugar and drug addiction.
References


Figure and table legends

Table 1
Mean (sem) total consumption of rat chow and HFCS in non-food restricted (Experiment 1) and food-restricted (Experiment 2) rats per 100g body weight. * = p<0.05.

Figure 1
Mean (sem) time spent in the naltrexone-paired compartment during the pre-conditioning and test sessions in rats given unlimited home cage access to 0% or 50% HFCS solutions and rat chow for 22 days prior to, as well as during, naltrexone (1 and 3 mg/kg) conditioning. * = p<0.05.

Figure 2
Mean (sem) time spent in the naltrexone-paired compartment during the pre-conditioning and test sessions in food-restricted rats given unlimited home cage access to 0% or 50% HFCS solutions for 22 days prior to, as well as during, naltrexone (1 and 3 mg/kg) conditioning. * = p<0.05.

Figure 3
Mean (sem) time spent in the naltrexone-paired compartment during pre-conditioning and test sessions in animals given acute intragastric infusions of HFCS (0, 0.5, 1, 2 g/kg), 30 minutes prior to naltrexone (1 mg/kg) conditioning. * = p<0.05.

Figure 4
Mean (sem) time spent in the naltrexone-paired compartment during pre-conditioning and test sessions in animals given 0 mg/kg/day or 3.5 mg/kg/day heroin via osmotic mini-pumps prior to, as well as during, naltrexone conditioning (1 mg/kg). * = p<0.05. ** =
p<0.05 time spent in the naltrexone-paired compartment between 0 mg/kg/day and 3.5 mg/kg/day heroin groups.

**Figure 5**

Mean (sem) time spent in the naltrexone-paired compartment during pre-conditioning and test sessions in animals given acute injections of 0 mg/kg or 2 mg/kg heroin 24 hours prior to naltrexone (1 mg/kg) conditioning. * = p<0.05. ** = p<0.05 time spent in the naltrexone-paired compartment between 0 mg/kg and 2 mg/kg heroin groups.
**Tables and Figures**

**Table 1**

Mean (sem) total consumption of rat chow and HFCS in Experiments 1 and 2.

<table>
<thead>
<tr>
<th></th>
<th>Rat chow (g)</th>
<th>HFCS (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experiment 1</strong></td>
<td>229.1 (4.1)</td>
<td>149.3 (11.3)</td>
</tr>
<tr>
<td><strong>Experiment 2</strong></td>
<td>164.9 (1.2)*</td>
<td>254.7 (2.7)*</td>
</tr>
</tbody>
</table>
Figure 1

The figure shows a bar graph comparing the mean (SEM) time spent in naloxone-paired compartments across different conditions. The x-axis represents the HFCS concentration (0% and 50%) and the Naltrexone dose (1 mg/kg and 3 mg/kg). The y-axis represents the mean (SEM) time spent in naloxone-paired compartments, ranging from 0 to 800 seconds. The graph includes two bars for each condition, one for pre-conditioning and one for test phases, with significant differences indicated by asterisks.
Figure 2
Figure 3
Figure 4
Figure 5
General Discussion

Overall, naltrexone failed to precipitate an affective withdrawal after acute and chronic HFCS pre-exposure. In contrast, heroin pre-exposure potentiated naltrexone-induced aversions representing a clear affective withdrawal. Motivational heroin withdrawal was likely a result of the inverse agonist properties of naltrexone within the extended amygdala. In naïve animals, naltrexone acts as MOR antagonist, but when opiate agonists are administered the properties of naltrexone change to that of an inverse agonist (Liu and Prather 2001; Shoblock and Maidment 2006). According to the two-state receptor theory this occurs because in naïve animals there is a fairly equitable balance between active and inactive receptors (Cruz et al. 1996). Morphine alters this equilibrium by increasing the number of active receptors, while naloxone/naltrexone precipitates withdrawal by rapidly shifting this equilibrium towards a state favoring inactive receptors causing the opposite effects of MOR agonism (Wang et al. 2001). The extended amygdala is a key neural substrate underlying naloxone/naltrexone-precipitated CPA in morphine treated animals. Increased c-fos and adenylate cyclase activity have been observed within the nucleus accumbens and extended amygdala in animals that show a CPA to naloxone after morphine pre-treatment (Valverde and Tzavara 1996; Gracy et al. 2001). In particular, the central nucleus of the amygdala (CeA) is thought to play a unique role in motivational component of opiate withdrawal because it is a key regulator of emotional processing (Verdejo-Garcia and Bechara 2009). Intracranial injections of MOR antagonists into the CeA cause an affective opiate withdrawal at doses that do not precipitate somatic signs (Stinus et al. 2002). Furthermore, naloxone given 24 hours post-morphine induces affective but not somatic signs of withdrawal that are
associated with increased c-fos gene expression in the CeA but not the shell of the nucleus accumbens or the bed nucleus of the stria terminalis (BST) (Jin et al. 2004). Thus, the CeA appears to be uniquely involved in the motivational component of morphine withdrawal. Due to the rapid conversion of heroin into morphine the motivational component of heroin withdrawal is likely mediated by similar mechanisms (Inturrisi et al. 1984).

Naltrexone also induced a CPA in naïve animals. The likely mechanisms underlying this effect are a decrease in endogenous opioid tonicity, due to competitive antagonism of opioid receptors (Narayanan et al. 2004). The role of opioidergic functioning in naltrexone-induced aversions is demonstrated by attenuation of naloxone-induced CPA in naïve animals that are deficient in MORs or enkephalins (Skoubis et al. 2001; Skoubis et al. 2005). Furthermore, intracranial injections of naloxone cause a CPA when injected directly into the ventral pallidum; a brain region highly involved in reward from drugs and natural reinforcers (Skoubis and Maidment 2003). Thus, naltrexone likely causes an aversion by blocking enkephalin binding on MORs within the ventral pallidum, resulting in an aversive state due to disruption of basal hedonic tonicity. Additionally, it is likely that the amygdala and ventral pallidum interact during naltrexone-precipitated heroin withdrawal, in addition to aversions in naïve animals.

There are several limitations in the current study. First, MOR antagonism may not be the most appropriate pharmacological approach for precipitating HFCS withdrawal. In addition to opioid systems, dopaminergic mechanisms are also activated by consumption of sugars along with non-monoaminergic processes related to energy regulation (Schulingkamp et al. 2000; Hajnal and Norgren 2001). However, somatic withdrawal has
been precipitated with naloxone, indicating that at least some aspects of sugar withdrawal are related to opioid activity (Colantuoni et al. 2002). This is in contrast to opiates, which precipitate both affective and somatic withdrawal through antagonism of opioid receptors (Bechara et al. 1995). In addition, debate exists as to whether withdrawal like behaviors observed in animals that have had sugar removed are instead related to energy deficits (Meule and Gearhardt 2014). In our study, precipitation of HFCS withdrawal with mu-opioid receptor antagonism allows for investigation of withdrawal without direct metabolic manipulations. Future research, will determine whether the psychological aspect of sugar withdrawal is mediated by different mechanisms.

Second, different routes of administration were involved in sugar and drug ingestion. Specifically, chronic unlimited HFCS was voluntarily consumed in the animals’ home cage, which differs from the administration of heroin subcutaneously through osmotic mini-pumps or injections. This may have affected withdrawal because animals self-administering heroin demonstrate a greater tendency to “relapse” compared to animals that are passively infused with the drug (Leri and Stewart 2002). However, while the method of administration differs between heroin and HFCS, oral ingestion of sugars is the primary method of sugar intake in nearly all species, while drugs of abuse are often administered subcutaneously (Volkow and Wise 2005; Roth et al. 2015). Thus, the pharmacokinetic properties of heroin and HFCS in the current study are similar to that seen with human users.

Third, acute administration of HFCS and heroin were only given prior to naltrexone conditioning sessions. This may have attenuated aversions to naltrexone due to the rewarding properties of HFCS and heroin. However, both sugars and drugs were
administered in this way, which allows for a comparison of affective withdrawal between these two substances. Furthermore, this methodology is similar to research showing affective withdrawal with morphine administered 24 hours prior to only naltrexone conditioning (Parker and Joshi 1998).

Fourth, chronic heroin was released during naltrexone conditioning while animals did not have access to HFCS after they received injections of naltrexone in the conditioning chambers. Thus, during antagonism of MOR, HFCS may not have been as readily available in the blood as heroin. Furthermore, heroin binds directly to MOR’s while sugar activates them indirectly by increasing endogenous opioids. Therefore, heroin released during conditioning may have potentiated the aversive effects of naltrexone. However, acute HFCS was administered 30 minutes prior to naltrexone conditioning, and was timed to correspond with peak blood glucose levels. In contrast, acute heroin was administered 24 hours prior to naltrexone conditioning a time point when its peak agonist effects have subsided (Skoppl and Ganssmann 1997). Thus, it is unlikely that differences in naltrexone-induced aversions were due to the release of heroin but not sugar during conditioning.

Despite these limitations, the current research raises questions regarding the validity of the food addiction hypothesis. Specifically, the lack of an affective HFCS withdrawal highlights different neurobehavioural actions of drugs and sugar. According to the food addiction hypothesis, because affective drug withdrawal is well documented, it would be expected that similar aversive states occur with the consumption of highly palatable foods. However, in humans limited evidence of sugar withdrawal and tolerance have been documented, and when presented they are in the form of self-reported
symptoms (Gearhardt et al. 2009; Kenny 2013). Thus, the primary evidence for sugar withdrawal comes from animal research, but a number of questions have been raised as to the external validity of these findings. For instance, evidence of somatic signs of sugar withdrawal is only found with intermittent access schedules that promote binge eating, which is a core characteristic of Binge Eating Disorders (BED) (Avena 2010). This subcategory of eating pathology has shown good correlation with a number of measures of food addiction, yet there is not a complete overlap (Gearhardt et al. 2012; Granero et al. 2014). Furthermore, only a portion of individuals with obesity suffer from BED (Gearhardt et al. 2012). Therefore, it is unclear whether this specific model of sugar consumption in laboratory animals can be applied to all aspects of the food addiction hypothesis. Thus, evidence from both humans and animals fail to provide clear examples of similarities between sugar and drug withdrawal.

In conclusion, the current research raises questions as to whether unhealthy eating habits are truly addictive like behaviors. A major problem with classifying individuals with pathological food consumption as “addicts” is that it takes the onus away from environmental conditions that promote caloric overconsumption. Instead the problem is focused around a select few individuals who are said to be “addicted” to food, instead of understanding corporate advertising tactics and cultural practices that promote problematic eating patterns (Gearhardt et al. 2009). Therefore, in moving forward it is important to understand both the environmental and biological components of food and the impacts it has on behavior. Furthermore, while a number of studies have identified similarities between foods and drugs, the current study highlights differences in
withdrawal. Thus, both distinct and overlapping aspects of food and drug addiction should to be taken into account when trying to diagnose and treat unhealthy eating habits.
References


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