Neuropharmacology 135 (2018) 547–554

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Bupropion and naltrexone combination alters high fructose corn syrup self-administration and gene expression in rats

AnneMarie Levy [a, 1], Stephen Daniels [a, 1], Roger Hudson [a], Thomas Horman [a], Amanda Flynn [a], Yan Zhou [b], Francesco Leri [a, *]

[a] University of Guelph, Guelph, Ontario, Canada
[b] Laboratory of Addictive Diseases, Rockefeller University, New York, USA

ARTICLE INFO

Article history:
Received 20 September 2017
Received in revised form
18 January 2018
Accepted 24 January 2018

Keywords:
Bupropion
Naltrexone
High fructose corn syrup
Mu-opioid receptor
Brain derived neurotrophic factor
Pro-opiomelanocortin

ABSTRACT

Contrave® is an adjunct pharmacotherapy for obesity that contains bupropion (BUP) and naltrexone (NTX). To further explore the psychopharmacology of this drug combination, male Sprague-Dawley rats were implanted with subcutaneous osmotic mini-pumps releasing: 40 mg/kg/day BUP, 4 mg/kg/day NTX, or 40 + 4 mg/kg/day BUP and NTX (BN). During 12 days of exposure, the animals were tested on operant intraoral self-administration (IOSA) of high fructose corn syrup (HFCS) on continuous (FR1) and progressive ratio (PR) schedules, on home cage drinking of HFCS, and on HFCS taste reactivity. Locomotion activity was also assessed. At the conclusion of the study, mRNA expression of genes involved in reward processing, appetite and mood were quantified. It was found that BN produced effects that could largely be ascribed to either BUP or NTX independently. More specifically, BN-induced reductions of HFCS IOSA on a FR1 schedule and home cage drinking, as well as alterations of MOR and POMC mRNA in the nucleus accumbens core and hypothalamus respectively, were attributable to NTX; while alterations of hippocampal BDNF mRNA was attributable to BUP. But, there was also some evidence of drug synergy: only BN caused persistent reductions of HFCS IOSA and drinking; BN produced the least gain of body weight; and only BN-treated rats displayed altered D2R mRNA in the caudate-putamen. Taken together, these observations support the use of BUP + NTX as a mean to alter consumption of sugars and reducing their impact on brain systems involved in reward, appetite and mood.

© 2018 Elsevier Ltd. All rights reserved.

1. Introduction

Obesity, a primary cause of mortality and morbidity worldwide (Ng et al., 2013), can be curbed by lifestyle changes (Jensen et al., 2014) and by adjunct pharmacotherapy (Greig and Keating, 2015). Several drugs have been developed to reduce excessive eating and body-weight (Apovian et al., 2013), including an oral formulation containing extended release bupropion (BUP) and naltrexone (NTX). When used alone, BUP is typically employed as an antidepressant (Buoli et al., 2015) as well as a smoking cessation agent (Cryan et al., 2003), while NTX is prescribed for both obesity (Greig and Keating, 2015) and alcohol addiction (Thorsell, 2013). The formulation containing BUP and NTX (abbreviated in this report as "BN"), marketed with the trade name Contrave© (Sherman et al., 2016), has been found to reduce body weight, reduce cardiometabolic risk factors, and improve glycemic control (Greenway et al., 2009a; Greig and Keating, 2015).

The focus of the current study in laboratory animals is to explore psychopharmacological actions of Contrave® on obesogenic behaviours (Clapper et al., 2013). More specifically, this study was designed to test the hypothesis that Contrave® can decrease appetitive responses to nutritional incentive stimuli, and hence decrease caloric intake from highly palatable foods. It is known that obese individuals treated with this formulation report less cravings for palatable foods rich in sugar/starch, and more control over their drive to consume food (Greenway et al., 2010; McElroy et al., 2013). They also display decreased hypothalamic reactivity to food cues (Wang et al., 2014). Similarly, the synergistic reduction of food consumption induced by the co-administration of BUP and NTX in laboratory rats (Wright and Rodgers, 2013) can be observed when the drugs are infused directly into the ventral tegmental area, a

* Corresponding author. Department of Psychology and Neuroscience, University of Guelph, Guelph, N1G 2W1, Ontario, Canada.
E-mail address: fleri@uoguelph.ca (F. Leri).
[1] Contributed equally.

https://doi.org/10.1016/j.neuropharm.2018.01.035
0028-3908/© 2018 Elsevier Ltd. All rights reserved.

brain region involved in the modulation of responses to motivationally salient stimuli (Sinnayah et al., 2012). However, because nausea is a common side effect of Contrave® (Greig and Keating, 2015), it is possible that reductions in caloric intake could also result from changes in perceived palatability of food. Additionally, because BUP is a psychomotor stimulant (Wright and Rodgers, 2013), it may be that body weight is reduced by augmented energy expenditure.

Therefore, three independent experiments were conducted using different procedures to assess the generalizability of possible behavioral and gene expression effects. Experiment 1 compared the effects of BUP, NTX, and BN, on intraoral operant self-administration (IOSA; Levy et al., 2015) of HFCS using continuous (fixed ratio 1; FR1) and progressive ratio (PR) reinforcement schedules. These schedules were selected because they assess both consummatory and appetitive (Spealman and Goldberg, 1978; Arnold and Roberts, 1997) aspects of responses to incentive stimuli, respectively. HFCS was selected because of its widespread prevalence in food products, and because its consumption in rodents has been linked to several biomarkers of addiction (Levy et al., 2015). In Experiment 2, the drugs were tested in animals that also self-administered HFCS, but by drinking the solution from traditional sipper tubes, made available continuously, and in the absence of food restriction. Finally, Experiment 3 did not involve self-administration, and the effect of these drugs on HFCS palatability was assessed by measuring orofacial reactions in response to experimenter-delivered intraoral infusions of HFCS (Parker et al., 1992). Experiment 3 also assessed horizontal locomotion in activity chambers to reveal potential motor side effects of the drugs.

Finally, this study explored expression of targeted genes in the brain of rats exposed to HFCS and treated with BUP, NTX and BN. More specifically, the D2 dopamine receptor (D2R) in the caudate-putamen and the mu-opioid receptor (MOR) in the nucleus accumbens (core subdivision) have been involved in addictive behaviors (Daglish et al., 2008; De Vries and Shippenberg, 2002), and their mRNA expression was assessed in Experiment 1 because both genes were affected by HFCS intraoral self-administration (Levy et al., 2015). In Experiment 2, rats could consume much more HFCS because it was made available *ad libitum* in their home cages, hence POMC mRNA in the hypothalamus was assessed to verify the purported therapeutic effect of BN in individuals with binge eating disorders (Gearhardt et al., 2012). In the same animals, brain derived neurotrophic factor (BDNF) mRNA expression in the hippocampus (CA1, CA3 and dentate gyrus) was also quantified because it is considered a biomarker of anhedonia and depression (Lee and Kim, 2010), and Contrave® has been reported to relieve mood disorders in obese individuals (Hausenloy, 2009). A control group not exposed to HFCS and treated with vehicle was also included to interpret the mRNA data.

2. Experimental methods

2.1. Subjects

Adult male Sprague-Dawley rats (Charles River, St-Constant, QC, Canada) weighing 200–250 g were single-housed with standard environmental enrichment, maintained on reverse light/dark cycle (7:00 a.m. lights off, 7:00 p.m. lights on), and tested during the active phase. Unless otherwise indicated, rats had *ad libitum* access to standard laboratory chow and water in their home cages. All experiments were approved by the Animal Care Committee of the University of Guelph and carried out in accordance with the recommendations of the Canadian Council on Animal Care.

2.2. Surgery

2.2.1. Osmotic mini-pumps

Subcutaneous osmotic mini-pumps (Alzet model 2ML2, 0.5 μl/hour for 12 days, Durect Corporation, Cupertino, CA, USA) were surgically implanted and removed as described in Leri et al. (2006). All behavioral testing was conducted 24 h after pump insertion.

2.2.2. Intraoral cannulation

Intraoral cannulas were surgically implanted as described in Levy et al. (2014).

2.3. Apparatus

2.3.1. Operant intraoral self-administration (IOSA)

IOSA of HFCS occurred in 26 operant chambers (model ENV-008CT, Med Associates, Lafayette, IN) equipped with retractable levers configured for intraoral infusions as described in Levy et al. (2015).

2.3.2. Home cage consumption

Home cage consumption of HFCS was assessed using 100 ml no-drip water bottles (Thermo Scientific, Waltham, MA, USA) with metal spouts (Ancare, Bellemore, NY, USA) secured with rubber stoppers (Fisher Scientific, ON, Canada) placed alongside standard water bottles as described in Daniels et al. (2016). Chow consumption was measured daily by weight, and care was taken to collect any food found on the floor of the cage.

2.3.3. Locomotion chambers

Horizontal and vertical activity was automatically tracked using EthoVision (v3, Noldus, The Netherlands) in 12 semitransparent Plexiglas chambers ($30.0 \times 40.0 \times 26.0$ cm; University of Guelph, ON, Canada).

2.3.4. Taste reactivity

Orofacial reactions (i.e., taste reactivity test) were assessed in clear Plexiglas chambers ($22.5 \times 26.0 \times 20.0$ cm) placed over a transparent glass surface. A digital video camera (Sony, DCR-HC48) was pointed at a mirror slanted on a 45° angle under the glass to visualize the ventral surface of the rat. The tapes were later scored under blind experimental conditions in slow motion (1/2 time) for the number of tongue protrusions, which were operationalized as the number of times the rat extended its tongue from its mouth over the 60-s taste reactivity test (Observer v12, Noldus, The Netherlands) (Levy et al., 2015).

2.3.5. Solution hybridization RNase protection-precipitation assay

Animals were euthanized using CO^2 6 days after termination of drug administration to allow for complete recovery from mini-pump removal surgery, clearance of all drugs, and alignment with previous experiments conducted in our laboratory. Brains were collected and the areas of interest were dissected on ice and stored at −80 °C for mRNA quantification (attomoles/μg) using a solution hybridization RNase protection-TCA precipitation protocol described in Leri et al. (2006). Regions of interest included D2R mRNA in the caudate-putamen, which is usually reduced in addictive diseases (Shumay et al., 2012; Dobbs et al., 2017; Leri et al., 2009, 2012). MOR mRNA in the nucleus accumbens was quantified in the core subdivision because our laboratory has previously observed alterations of this gene only in the core (Levy et al., 2015). Finally, POMC mRNA was quantified in the hypothalamus, and BDNF mRNA was quantified in a combination of hippocampal tissue including CA1, CA3 and dentate gyrus regions (Hudson et al., 2017).

Download English Version:

https://daneshyari.com/en/article/8516805

Download Persian Version:

https://daneshyari.com/article/8516805

Daneshyari.com