Cureus

Open Access
Poster

Cureus

Bupropion and Naltrexone Interact Synergistically to Decrease Food Intake in Mice

Orexigen Therapeutics

1.

Corresponding author: Orexigen Therapeutics, orexigen.therapeutics@cureus.com

Categories: Endocrinology/Diabetes/Metabolism
Keywords:

How to cite this poster
Therapeutics O (2012) Bupropion and Naltrexone Interact Synergistically to Decrease Food Intake in Mice. Cureus 4(10): e205.

Abstract

Proopiomelanocortin (POMC) neurons in the hypothalamus are activated by the adipose hormone leptin, and produce alpha-melanocyte stimulating hormone (in-MSH) which binds to and activates melanocortin-4 receptors, causing reduced food intake and increased energy expenditure. However, in obesity these circuits are leptin resistant. POMC neurons are inhibited by opioids via a mu opioid receptor. We and others have previously shown that dopamine (DA) activates POMC neurons. Here we explore the mechanistic basis for combination of bupropion (BUP), a dopamine (DA) and norepinephrine (NE) reuptake inhibitor and naltrexone (NAL), an opiod antagonist as a therapeutic approach to activate the melanocortin circuits and treat obesity. We tested the possibility that the effects of BUP, NAL and combination of BUP + NAL are mediated through POMC neurons. We evaluated the effects of DA, BUP, NAL, DA + NAL and BUP + NAL on neuronal activation and feeding behavior in mice. Electrophysiological studies indicated that DA, BUP, NAL, DA + NAL, and BUP + NAL increased the frequency of action potentials in POMC neurons. For feeding studies, fasted lean and obese mice (Diet-induced obese or DIO) were given ad libitum access to a predetermined amount of food immediately after intraperitoneal (IP) injection with BUP, NAL, BUP + NAL or vehicle. In lean mice, treatment with BUP, NAL or BUP + NAL caused a 34%, 67% and 77% inhibition of food intake, respectively. In DIO mice treatment with BUP, NAL or BUP + NAL caused a 27%, 49% and 94% inhibition of food intake, respectively. The interaction between BUP and NAL appeared more potent in DIO mice than in lean mice. Isobolographic analysis indicated that BUP + NAL most likely interacts in a synergistic manner in obese mice. BUP and NAL regulate dopamine and opioid signaling, which play critical roles in the mesolimbic reward pathways (ventral tegmental area or VTA). Furthermore, both BUP and NAL are separately used for the treatment of addictive disorders. We microinjected BUP, NAL and BUP +NAL into the VTA and measured subsequent food intake. Intra-VTA BUP + NAL caused a clearly synergistic decrease in food intake in lean hungry mice. These data provide a mechanistic rationale for the treatment of obesity with combination therapy of BUP + NAL, and support the hypothesis that BUP + NAL will influence rewarding aspects of food.

Open Access
Published 10/01/2012

65