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Research report

A new biomarker of hedonic eating? A preliminary investigation of cortisol and nausea responses to acute opioid blockade ☆

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ABSTRACT

Overweight and obese individuals differ in their degree of hedonic eating. This may reflect adaptations in reward-related neural circuits, regulated in part by opioidergic activity. We examined an indirect, functional measure of central opioidergic activity by assessing cortisol and nausea responses to acute opioid blockade using the opioid antagonist naltrexone in overweight/obese women (mean BMI = 31.1 ± 4.8) prior to the start of a mindfulness-based intervention to reduce stress eating. In addition, we assessed indices of hedonic-related eating, including eating behaviors (binge eating, emotional eating, external eating, restraint) and intake of sweets/desserts and carbohydrates (Block Food Frequency); interoceptive awareness (which is associated with dysregulated eating behavior); and level of adiposity at baseline. Naltrexone-induced increases in cortisol were associated with greater emotional and restrained eating and lower interoceptive awareness. Naltrexone-induced nausea was associated with binge eating and higher adiposity. Furthermore, in a small exploratory analysis, naltrexone-induced nausea predicted treatment response to the mindfulness intervention, as participants with more severe nausea at baseline maintained weight whereas those with little or no nausea responses tended to gain weight. These preliminary data suggest that naltrexone-induced cortisol release and nausea may help identify individuals who have greater underlying food reward dependence, which leads to an excessive drive to eat. Future research is needed to confirm this finding and to test if these markers of opioidergic tone might help predict success in certain types of weight management programs.

Introduction

With the advent of the obesity epidemic and the abundance of palatable foods in the current food environment, the concept of hedonic eating has emerged. Hedonic eating refers to eating for the pleasurable, rewarding aspects of food, in contrast to homeostatic eating, which refers to eating for caloric need (Lowe & Butryn, 2007). Hedonic eating has been implicated in the concept of "food addiction," the existence of which is being hotly debated in scientific and public discourses (Avena, Gearhardt, Gold, Wang, & Potenza, 2012; Ziauddeen, Farooqi, & Fletcher, 2012). Theorists propose that hedonic-driven eating can cause people to become addicted to food or its specific components in ways that resemble drug addiction (Davis, Zai, et al., 2011; Moreno & Tandon, 2011). In turn, these eating behaviors may lead to weight gain and obesity in a subset of individuals.

Evidence supporting the concept of food addiction is accruing as neuroimaging studies reveal that both obese and drug addicted individuals have alterations in brain regions associated with reward sensitivity, incentive motivation, memory and learning, impulse control, stress reactivity, and interoceptive awareness (for a review, see Volkow, Wang, Fowler, Tomasi, & Baler, 2011). In animal studies, growing evidence indicates that palatable foods prevalent in our food supply (in particular, those containing high levels

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of sugar and fat) possess addictive properties. Rats given access to highly palatable foods display classic features of addiction, including binging, withdrawal, craving, and cross-sensitization as found in response to drugs of abuse (Avena, 2010).

The opioid system is in part contained within an important neural circuit involved in both substance use and food reward. Acute consumption of palatable food stimulates release of endogenous opioids, which mediate feelings of pleasure (Yeomans & Gray, 2002). However, repeated over-stimulation of post-synaptic opioid receptors due to chronic intake of palatable foods may elicit long-term changes in receptor function or transduction mechanisms that subsequently down-regulate opioid action (Kelley, Will, Steininger, Zhang, & Haber, 2003). For instance, rats given frequent access to chocolate or sucrose that elicit binge eating behaviors show reduced expression of enkephalins (an endogenous opioid) in the ventral striatum, a brain region involved in reward (Kelley et al., 2003; Spangler et al., 2004). The resulting opioidergic state may induce a state of withdrawal. Rats given chronic access to a high sucrose diet and then either abruptly taken off or treated with an opioid antagonist demonstrate behaviors consistent with opiate withdrawal (Colantuoni et al., 2002). A withdrawal state, in turn, can increase incentive salience for sugar, as found in alcohol abuse (Avena, Long, & Hoebel, 2005). The "wanting" of a food reward is mediated through μ-opioid signaling in the nucleus accumbens (Shin, Pistell, Phifer, & Berthoud, 2010). These various animal studies demonstrate that central opioid activity is involved in core addiction processes related to palatable foods, in particular, bingeing, withdrawal, and craving.

Despite compelling neurobiological models of addiction in animals, there is a paucity of direct evidence to validate the concept of hedonic-driven eating or food addiction in humans (Ziauddeen & Fletcher, 2013). There are no validated functional markers of central opioidergic activity in humans, short of positron-emission tomography (PET) scans to assess opioid receptor binding potential. However, as an indirect functional measure, the effects of opioid antagonists on the hypothalamic–pituitary–adrenal axis (HPA) have been studied to assess the role of endogenous opioidergic activity in alcohol and nicotine addictions (e.g., al'Absi et al., 2008; Ouwens, van Strien, van Leeuwe, & van der Staak, 2009; Wand, Mangold, El Deiry, McCaul, & Hoover, 1998; Wand et al., 2012). Endogenous opioids inhibit the HPA axis through two pathways. First, neurons in the arcuate nucleus containing β-endorphin and enkephalin activate μ-opioid receptors in the paraventricular nucleus to inhibit corticotropin releasing-hormone (CRH) release (Yajima et al., 1986). Opioids also inhibit the activity of norephinephrine-containing neurons in the locus coeruleus, which activate hypothalamic CRH neurons (Valentino, Rudoy, Saunders, Liu, & Van Bockstaele, 2001). Phamacologic blockade of opioid receptors releases the opioidergic inhibitory input to CRH neurons, stimulating pituitary adrenocorticotropic hormone (ACTH), and eventually cortisol from the adrenal glands. As a result, individual differences in central opioidergic activity can be detected by cortisol response to opioid antagonism. Greater increases in cortisol release to an opioid antagonist may indicate weaker endogenous opioid tone as a result of fewer endogenous opioids available to compete for binding sites, or a reduction in opioid receptor density resulting in a more complete blockade of inhibitory inputs to the hypothalamus (Roche, Childs, Epstein, & King, 2010; Wand et al., 1998). Thus far, one study found that patients with bulimia had higher cortisol levels in response to naloxone (an opioid antogonist) as compared to controls (Coiro et al., 1990).

While the exact mechanisms underlying the association between cortisol responses, central opioidergic activity, and opioid antagonists are unknown, we theorized that chronic overconsumption of highly palatable foods downregulates endogenous opioid peptide production or receptor density, which would be reflected by increased cortisol in response to an opioid antagonist. We also postulated that nausea responses to opioid antagonism may be a second indicator of central opioid activity, as those with low opioidergic tone may feel more nauseous after acute opioid blockade. Naltrexone therapy (primarily a μ-opioid antagonist) in combination with bupropion results in clinically significant weight loss (Apovian et al., 2013) supporting the role of the opioid system in eating behavior and weight gain. Yet nausea is a common side effect of naltrexone, and a qualitative review suggests it may be increased in persons with obesity (Yeomans & Gray, 2002). In two large clinical trials that administered naltrexone to obese individuals, 30–34% reported nausea in the drug therapy condition compared to 5–11% in the placebo group (Katsiki, Hatzitolios, & Mikhailidis, 2011). Thus far, the relationship between naltrexone-induced nausea and hedonic-related eating remains unexplored.

In the current study, we assessed cortisol and nausea responses to a standardized naltrexone challenge among overweight and obese women. In cross-sectional analyses, we tested if these responses were associated with hedonic-related eating behaviors, including binge, emotional, and external-based eating. We also examined dietary restraint because, although it does not explicitly measure hedonic eating, people high on restraint overeat in the face of stress or cognitive load (Lowe & Kral, 2006). Dietary restraint has also been recently re-conceptualized as reflecting a latent hedonic eating drive, with highly restrained individuals eating less than they want, rather than less than they need (Lowe & Butryn, 2007). We also assessed the relation between cortisol and nausea responses to naltrexone with dietary intake and adiposity. When given naltrexone, women reporting higher levels of hedonic-related eating behaviors may demonstrate a more severe opiate-like withdrawal state, similar to the rat model of high sugar intake (Colantuoni et al., 2002). Therefore, we predicted greater nausea and cortisol responses to naltrexone, presumably indicating weaker opioidergic activity, would be associated with higher levels of hedonic-related eating behaviors, greater intake of palatable foods, and excess adiposity.

We also explored the association of naltrexone responses with interoceptive awareness, the perception of sensations originating from inside the body. According to recent theories, interoceptive awareness is important for regulating homeostasis and may be altered as a result of addiction (Goldstein et al., 2009; Naqvi & Bechara, 2010; Paulus, Tapert, & Schulteis, 2009). Because addicted individuals chronically experience aversive bodily states either resulting from withdrawal symptoms or emotional distress, they may react more impulsively to sensations of craving or withdrawal either to satisfy urges or alleviate the aversive state (Paulus et al., 2009). As a first step towards understanding the potential relation between opioid-mediated food addictive processes and interoceptive awareness, we examined whether self-reported aspects of interoceptive awareness were related to naltrexone responses.

Lastly, responses to acute opioid blockade may have clinical utility by predicting individual differences in treatment response to interventions for overweight and obese individuals. We explored whether naltrexone responses at baseline predicted weight change among women enrolled in a randomized waitlist-control pilot study of a mindfulness-based intervention for stress eating (Daubenmier et al., 2011).

Methods

Participants

This paper reports on baseline data collected from a subset of women ($N = 33$) who elected to participate in a substudy of a randomized waitlist control pilot trial of a mindfulness intervention