Putting the brakes on the "drive to eat": Pilot effects of naltrexone and reward-based eating on food cravings among obese women

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ABSTRACT

Purpose: Obese individuals vary in their experience of food cravings and tendency to engage in reward-driven eating, both of which can be modulated by the neural reward system rather than physiological hunger. We examined two predictions in a sample of obese women: (1) whether opioidergic blockade reduced food-craving intensity, and (2) whether opioidergic blockade reduced an association between food-craving intensity and reward-driven eating, which is a trait-like index of three factors (lack of control over eating, lack of satiation, preoccupation with food).

Methods: Forty-four obese, pre-menopausal women completed the Reward-Based Eating Drive (RED) scale at study start and daily food-craving intensity on 5 days on which they ingested either a pill-placebo (2 days), a 25 mg naltrexone dose (1 day), or a standard 50 mg naltrexone dose (2 days).

Results: Craving intensity was similar under naltrexone and placebo doses. The association between food-craving intensity and reward-driven eating significantly differed between placebo and 50 mg naltrexone doses. Reward-driven eating and craving intensity were significantly positively associated under both placebo doses. As predicted, opioidergic blockade (for both doses 25 mg and 50 mg naltrexone) reduced the positive association between reward-driven eating and craving intensity to non-significance.

Conclusions: Opioidergic blockade did not reduce craving intensity; however, blockade reduced an association between trait-like reward-driven eating and daily food-craving intensity, and may help identify an important endophenotype within obesity.

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1. Introduction

The modern food environment is replete with cues to eat highly palatable foods for the rewarding properties of eating, yet individuals vary in susceptibility to hedonic eating. Susceptible individuals have poor inhibitory control and heightened cravings, which can lead to compulsive overeating and weight gain (Epel et al., 2014; Volkow, Wang, & Baler, 2011). We recently validated the Reward-Based Eating Drive (RED) Scale, which assesses a lack of control over eating, lack of satiation, and preoccupation with food. The RED scale predicts weight gain and correlates with, but is distinct from, other non-pathological eating behavior scales [e.g., Power of Food Scale (Cappelleri et al., 2009)].

Reward-based eating is less likely to result from activation of neural circuitry of the hypothalamus (signaling hunger) than from the nucleus accumbens (signaling food reward) (Epel et al., 2014; Franken & Muris, 2005; Volkow, Wang, Fowler, Tomasi, & Baler, 2012; Volkow et al., 2011). Chronic consumption of highly processed, palatable, and arguably addictive foods may alter the endogenous opioid system (Volkow, Wang, Tomasi, & Baler, 2013; Volkow et al., 2011). In turn, these alterations may increase susceptibility to, and bias experiences of, opioid-mediated food cravings, which are often for these highly palatable foods (Christensen, 2007; Gearhardt, Rizk, & Treat, 2014). Indeed, a fast-growing literature, mainly rooted in animal studies, highlights associations among food craving, reward sensitivity, and opioid-mediated pathways in the neural experience of reward (Cota, Tschöp, Horvath, & Levine, 2006; Kirkham, 2009; Schneider, Heise, & Spanagel, 2010; Tetley, Brunstrom, & Griffiths, 2010).

Acute consumption of highly palatable food stimulates release of endogenous opioids (Colantuoni et al., 2002; Peciña & Smith, 2010).

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Conversely, opioid antagonists (e.g., naloxone) can suppress this action, as evidenced by reductions in rodents' consumption of palatable food (Boggiano et al., 2005; Pijlman, Wolterink, & Van Ree, 2003). Similarly, acute administration of opioid antagonists to people with prior opioid addiction histories (Langleben, Busch, O'Brien, & Elman, 2012) and obese men (Langleben et al., 2012; Spiegel et al., 1987) can result in reduced short-term cravings for, hedonic responses to, and consumption of, highly palatable food.

Chronic over-consumption of palatable food can dampen endogenous opioid action. Rodents chronically consuming a highly palatable diet that are either removed from the diet or administered an opioid antagonist demonstrate opioid-withdrawal behavior (Colantuoni et al., 2002). Similarly, women reporting more emotional or binge eating also report symptomology consistent with opioid withdrawal when under opioidergic blockade (Daubenmier et al., 2014).

Probing associations between reward-driven eating and food cravings by antagonizing the endogenous opioid pathway may reveal the extent to which food cravings are opioid-mediated. This could suggest targets for pharmacological or behavioral interventions for individuals who binge eat (McElroy, Guerdjikova, Mori, & O'Melia, 2012; Wang et al., 2014), who are obese, or who are at risk for weight gain. Indeed, several trials indicate that although naltrexone is not an efficacious monotherapy for obesity or binge eating (Greenway et al., 2009, Dec 1; McElroy et al., 2011), the combination of naltrexone and bupropion has resulted in clinically meaningful weight loss in some patients (Caixàs, Albert, Capel, & Rigla, 2014, Sep 18; Yanovski & Yanovski, 2015, Mar 24).

In a sample of obese women, we conducted two sets of secondary analyses. First, we predicted that opioidergic blockade by naltrexone would reduce food-craving intensity relative to placebo. Second, we predicted that opioidergic blockade would reduce the association between trait-like reward-driven eating and daily food-craving intensity, relative to placebo. We also explored whether this association would differ between standard (50 mg) and smaller (25 mg) naltrexone doses.

2. Methods

2.1. Participants

We recruited 44 obese community dwelling, English speaking, healthy, pre-menopausal women using flyers displaying a study website and phone number (M age = 32.7 years, SD = 7.6 years; M BMI = 34.5; SD = 3.3). Participants were 34.1% White, 31.8% Black, 15.9% Asian, 11.4% Mixed Race/Other, and 6.8% Hispanic. At a university medical center, potential participants completed laboratory blood and urine screens for pregnancy, diabetes, anemia, and liver function, and a psychological screen for mental disorders. Inclusion criteria included female sex, overweight status (30 ≤ BMI ≤ 40), and age of 20–45 years. Exclusion criteria included diabetes, current pregnancy or breastfeeding, smoking, medication, historical or current mental disorder or mental health treatment,[1] kidney or liver disease, illegal drug use or substance misuse, or contraindications to naltrexone (Center for Substance Abuse, 2009). Participants were financially compensated for participating. This trial is registered at clinicaltrials.gov (NCT01175512).

2.2. Procedure

The UCSF Institutional Review Board approved all study procedures. All participants provided written informed consent. Participants gave consent and completed questionnaires assessing demographics and eating behavior on day 0. We gave participants five identical-appearing pills labeled A thru E: two each of placebo and 50 mg naltrexone, and one of 25 mg naltrexone. Study staff and participants were told that

pill ordering was randomized and were masked to pill ordering. Participants were instructed which pill to take as close as possible to 1:00 PM (after lunch) on days 1 (placebo), 4 (25 mg naltrexone), 7 (placebo), 10 (50 mg naltrexone), and 4 weeks after day 10 (50 mg naltrexone). Participants recorded their exact time of ingestion and completed self-report items in paper logbooks, which they returned by mail.

2.3. Materials and measures

2.3.1. Study drug

Participants ingested either 25 mg or 50 mg of naltrexone hydrochloride, (ReVia; Teva, North Wales, PA), or a placebo pill. The FDA-approved dose for treatment of alcohol and opioid dependence is 50 mg, which has been recently used to investigate eating behavior (Center for Substance Abuse, 2009). Naltrexone has a mean elimination half life (T-1/2) of approximately 4 h. Participants recorded ingestion time on each study day in their logbook.

2.3.2. Reward-Based Eating Drive (RED) scale

Participants completed the 9-item RED scale, which assesses a loss of control over eating, a lack of satiety, and preoccupation with food. Sample items include: *When I start eating, I just can't seem to stop* (lack of control); and *I don't get full easily* (lack of satiety). Participants rated items on a scale from 1 (*strongly disagree*) to 5 (*strongly agree*). Items were summed, with higher scores reflecting higher Reward-Based Eating Drive (M RED = 8.21, SD = 5.03, Cronbach's α = .90).

2.3.3. Food-craving intensity

Just before bedtime each study day, participants recorded the time and retrospectively reported in their logbook their food-craving intensity that day. Participants first completed a dichotomous screening item, "*Did you experience a craving for a certain food today?*" If the participant endorsed "*yes*," she then answered the craving intensity item, "*how strong was your craving?*" on a Likert scale from 1 (*very weak*) to 5 (*very strong*).

2.3.4. Nausea

Nausea symptoms can follow naltrexone ingestion (Yeomans & Gray, 2002) with peak concentrations 2–3 h after administration. We therefore included nausea as a covariate. Participants self-reported nausea on a scale from 0 (*none*) to 3 (*severe*) hourly from 1:00–5:00 PM and then at bedtime each day in their logbooks. We coded women as experiencing nausea if they endorsed nausea at any timepoint (e.g., Center for Substance Abuse, 2009).

2.3.5. Statistical analyses

We used repeated-measures ANOVA to test for differences in craving intensity between all three study doses (average across the two placebo days vs. 25 mg naltrexone day vs. average across the two 50 mg naltrexone days). We used a generalized estimating equations (GEE) model to test whether dose (placebo vs. 25 mg naltrexone vs. 50 mg naltrexone) moderated an association between RED and craving intensity. GEE analysis can tolerate missing data and allows for maximum data retention. Our GEE analysis utilized an exchangeable correlation structure, which takes into account within-person dependence (Twisk, 2004). We used a series of dummy codes for dose (0, 1). We used multiple linear regression to conduct follow-up tests of associations between RED and craving intensity on each study day. All analyses accounted for age, BMI, and nausea.[2] We conducted all analyses in SPSS Statistics Version 22.

3. Results

Descriptive statistics appear in Table 1. Of 44 women who enrolled in the study, 5 provided no pill ingestion times or logbook responses, leaving

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[1] Though we excluded participants who met DSM-IV-TR criteria for bulimia, we did not exclude potential participants who reported binge eating.

[2] Results are unchanged regardless of covariate inclusion.

an analytic sample of 39. On average, participants reported ingesting study pills at 1:07 PM ($SD = 13$ min). As directed, participants recorded craving intensity on each study evening (on average, between 10:00–10:15 PM). Approximately one-third or fewer participants endorsed any nausea on any study day (Table 1), which is similar to previous reports of naltrexone nausea responses (Yeomans & Gray, 1996; Yeomans & Gray, 1997; Yeomans & Gray, 2002).

Repeated measures analysis showed that placebo, 25 mg, and 50 mg doses did not differentially impact craving intensity, $F(2, 5.82) = 1.19$, $p = .441$. GEE analysis; however, revealed a dose × RED interaction such that the association between RED and craving intensity differed between the placebo and 50 mg doses [$b = -0.06$, SE(b) = 0.02, 95% CI (-0.099, -0.012), $p = .012$]. The association between RED and craving intensity did not significantly differ between the placebo and 25 mg doses [$b = 0.05$, SE(b) = 0.05, 95% CI (-0.033, 0.142), $p = .224$] or the 25 mg and 50 mg doses [$b = -0.01$, SE(b) = 0.04, 95% CI (-0.084, 0.082), $p = .977$]. Multiple linear regression analyses examining each study day (Table 1; Fig. 1) revealed significant positive associations between RED and craving intensity on each placebo day ($p = .017$; $p = .034$) and non-significant associations on naltrexone days ($p = .433$; $p = .230$; $p = .215$).

4. Discussion

We used self-reported reward-driven eating (Epel et al., 2014) and a biological probe (Daubenmier et al., 2014) as a novel assessment method to identify obese women with increased opioid-mediated food cravings. We first found that naltrexone did not alter craving intensity in comparison to placebo: that is, craving intensity did not significantly differ between placebo, 25 mg naltrexone, and 50 mg naltrexone doses. Second, we found that opioidergic blockade reduced the association between reward-driven eating and craving intensity. Specifically, reward-driven eating and craving intensity were positively associated under placebo, and not significantly associated under 25 mg or 50 mg naltrexone. This suggests that reward-based eating may index an endophenotype reflecting greater opioid-mediated reward circuitry. We found some evidence of a dose–response effect of naltrexone such that the association between reward-driven eating and craving intensity did not significantly differ between (1) 25 mg and 50 mg or (2) placebo and 25 mg conditions; however, this association differed between (3) placebo and 50 mg conditions. Given these findings, we suggest that the standard 50 mg dose of naltrexone (versus placebo) may more clearly identify individuals with opioid-mediated food cravings.

That craving intensity did not significantly differ between placebo, 25 mg naltrexone, and 50 mg naltrexone doses suggests that craving intensity may not be predominantly opioid-mediated across all obese women. Rather, only obese women who report higher levels of reward-driven eating may have opioidergic alterations that underlie food cravings. These findings highlight the utility of characterizing individuals based on reward-driven eating. We note, however, that these results do not necessarily reflect changes in actual eating behavior in response to cravings. Assessing actual food intake will be key to determining clinical importance of these results.

Food cravings may be similar in intensity and neurobiological pathways to cravings observed in the context of drug addiction (Gearhardt
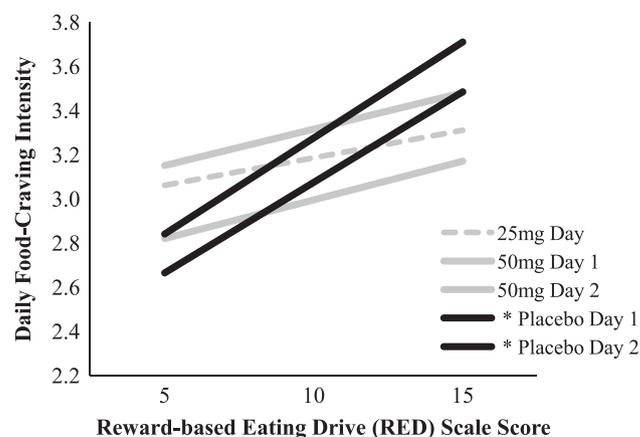
et al., 2011; Volkow et al., 2013). Individuals who tend toward reward-based eating may experience opioid-mediated cravings due to adaptations in reward-related brain circuitry (Berridge, Ho, Richard, & DiFeliceantonio, 2010; Castellanos et al., 2009; Davis et al., 2007) and fare worse in the modern obesogenic food environment (Lake & Townshend, 2006; Schäfer Elinder & Jansson, 2009), which continuously provides cues to overeat calorically dense, hyper-palatable foods. These results have implications for treatment matching: behavioral interventions targeting craving-related eating might be more effective among obese women who endorse more reward-driven eating.

This study has several limitations. Although the sample size is small, repeated measures analysis substantially increases statistical power to identify significant effects. We used an all-female sample, and although we did not control for menstrual phase or oral contraceptive status, recent data report that food cravings are similar across menstrual phases (McVay, Copeland, Newman, & Geiselman, 2012). Future research could consider targeting women in the luteal phase (Rozin, Levine, & Stoess, 1991; Tomelleri & Grunewald, 1987) to increase consistency and likelihood of observing craving experiences. Of the 39 participants who provided craving intensity data, three used oral contraceptives on three to five of five study days; however, data suggest that oral contraceptives do not significantly impact food cravings (Michener, Rozin, Freeman, & Gale, 1999; Tucci, Murphy, Boyland, Dye, & Halford, 2010). Additionally, we did not evaluate participants for the DSM-5 diagnosis of Binge Eating Disorder (BED); future studies should do so.

The out-of-laboratory study design assessed women among the food cues that they most encounter in their typical environments; future research could incorporate both in-laboratory and out-of-laboratory components. We did not randomize study medication days so as to limit attrition due to nausea or other side effects, and nausea experiences may have allowed participants to suspect they were receiving an active dose. Future studies should incorporate randomization while also considering potential attrition effects. As in daily diary methodologies (Iida, Shrout, Laurenceau, & Bolger, 2012), we used a single,

Note. * $p < .05$. See Table 1 for multiple regression model results.

Fig. 1. Associations between reward-based eating drive (RED) and food-craving intensity by study day.

Table 1
Multiple regression analyses predicting food-craving intensity from reward-driven eating.

Day	β	b (95% CI)	SE(b)	p	n (%) endorsing craving	n (%) endorsing nausea (of those endorsing craving)	M (SD) craving intensity°
Placebo (1)	0.57	0.03 (0.020, 0.178)	0.03	.017	21 (53.8%)	5 (12.8%)	3.24 (1.00)
Placebo (2)	0.56	0.04 (0.008, 0.185)	0.04	.034	21 (53.8%)	2 (5.1%)	3.22 (1.06)
Naltrexone 25 mg	0.20	0.04 (-0.066, 0.143)	0.04	.443	18 (46.2%)	7 (17.9%)	3.14 (0.85)
Naltrexone 50 mg (1)	0.33	0.03 (-0.028, 0.108)	0.03	.230	18 (46.2%)	14 (35.9)	3.33 (0.69)
Naltrexone 50 mg (2)	0.33	0.03 (-0.034, 0.125)	0.03	.215	19 (48.7%)	12 (30.8%)	3.05 (0.71)

Note. All models account for nausea (present vs. absent on that day), body mass index (BMI), and age. Significance and pattern of results do not change when we omit covariates. °Craving intensity did not significantly differ between days, per repeated-measures ANCOVA.

face-valid item amenable to repeated assessments that minimized participant burden, as we are not aware of a validated single-item measure of food-craving intensity.

Individuals with greater tendencies to eat for hedonic reward may experience cravings that are more difficult to resist. This is among the first studies to pair self-reported reward-driven eating with a biological index of hedonic eating drive (Daubenmier et al., 2014; Mason et al., 2015). Opioidergic blockade reduced a positive association between reward-driven eating and daily craving intensity, suggesting that food craving may be partially opioid-mediated. This unique methodology may help identify women who are particularly vulnerable to intense food cravings and highlight a potential neurobehavioral pathway contributing to obesity.

Contributors

Authors Epel, Adler, Kiernan, Laraia, and Gearhardt designed the study and wrote the protocol. Authors Mason, Puterman, and Daubenmier conducted the statistical analysis and interpreted the data. Authors Mason, Epel, and Daubenmier conducted literature searches. Author Mason wrote the first complete manuscript draft. Authors Adler, Epel, and Laraia obtained funding for the execution of this study. Authors Lustig, Dallman, and Hecht provided critical feedback and consultation on several drafts of the manuscript. Author Lustig prescribed study medication and was available throughout the study for medication-related issues.

Conflict of interest

Ashley E. Mason, Barbara Laraia, Jennifer Daubenmier, Frederick M. Hecht, Robert H. Lustig, Eli Puterman, Nancy Adler, Mary Dallman, Michaela Kiernan, Ashley Gearhardt, and Elissa S. Epel declare that they have no conflict of interest.

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