Oxytocin and Naltrexone Successfully Treat Hypothalamic Obesity in a Boy Post-Craniopharyngioma Resection

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Context: Hypothalamic obesity, a treatment-resistant condition common to survivors of craniopharyngioma (CP), is strongly associated with a poor quality of life in this population. Oxytocin (OT), a hypothalamic neuropeptide, has been shown to play a role in the regulation of energy balance and to have anorexigenic effects in animal studies. Naltrexone (NAL), an opiate antagonist, has been shown to deter hedonic eating and to potentiate OT’s effects.

Design: In this parent-observed study, we tested the administration of intranasal OT for 10 weeks (phase 1), followed by a combination of intranasal OT and NAL for 38 weeks (phase 2) in a 13-year-old male with confirmed hypothalamic obesity and hyperphagia post-CP resection. Treatment resulted in 1) reduction in body mass index (BMI) z score from 1.77 to 1.49 over 10 weeks during phase 1; 2) reduction in BMI z score from 1.49 to 0.82 over 38 weeks during phase 2; 3) reduced hyperphagia during phases 1 and 2; 4) continued hedonic high-carbohydrate food-seeking in the absence of hunger during phases 1 and 2; and 5) sustained weight reduction during decreased parental monitoring and free access to unlocked food in the home during the last 10 weeks of phase 2.

Conclusion: This successful intervention of CP-related hypothalamic obesity and hyperphagia by OT alone and in combination with NAL is promising for conducting future studies of this treatment-recalcitrant form of obesity. (J Clin Endocrinol Metab 103: 370–375, 2018)
effects on obese subjects (6), and research on nonhuman primates and humans has shown an effect of OT on weight loss (7) and improved social cognition (8). Among individuals with Prader-Willi syndrome who share many phenotypic traits with CP survivors, including social impairment, obesity, and hyperphagia (9), low-dose intranasal OT administration demonstrated multiple benefits, including reduction in appetite drive (10).

The corticolimbic and mesolimbic systems play a central role in regulation of eating behavior by mediating the rewarding aspects of food (11), and naltrexone (NAL), an opiate antagonist, has been shown to decrease subjective food pleasantness, eating rate (12, 13), and appetite in obese men (14). Studies in animals show NAL’s effect on reducing binge-like hyperphagia of highly palatable foods (15). In addition, opioids are known to decrease OT (16) whereas opiate antagonists, conversely, have been shown to increase the release of OT (17, 18) and potentiate the effects of OT (19).

Case Description

Pre-OT treatment period

At age 8, patient S underwent a transcranial gross total resection of a tumor identified as a multicystic and solid CP. No radiation treatment was performed. After the resection, S was diagnosed with visual impairment, adipism diabetes insipidus, adrenal insufficiency, thyroid deficiency, and growth hormone deficiency. In addition to panhypopituitarism, S developed hyperphagia and obesity soon after his tumor resection.

Similar to the experiences of many CP survivors, S exhibited pathological eating behaviors (3). Examples of S’s pretreatment hyperphagia included frequent complaints of hunger, middle-of-the-night eloping for food, stealing food, and stashing food. His obesity and intense drive for food prompted his family to monitor him closely on a low-fat (<20 g/d) diet and to keep all food under lock and key. To prevent risk of his overeating, S was denied access to social events, forbidden to enter grocery stores, not permitted to possess money, and never left alone. Despite his restricted access to food, his post-resection body mass index (BMI) remained in the obese range, between the 95th and 97th percentile. At age 12, over 1 year prior to commencing OT, S was placed on a low-carbohydrate (50 to 100 g/d) diet.

Due to patient S’s panhypopituitarism, obesity, hyperphagia, social impairment, poor quality of life, and lack of treatment options for these conditions, OT replacement was experimentally initiated as off-label use by his treatment team when he was 13 years old. His mother gave informed consent for the treatment and case report study. Intranasal OT was obtained from and compounded by Harbor Compounding Pharmacy (Costa Mesa, CA). The nonexistence of OT dosing studies of the treatment of patients with postresection CP HO led to the reliance on anecdotal evidence from patients with Prader-Willi syndrome who benefitted from low and intermittent intranasal OT treatment (in a conversation with Dr. Jennifer Miller in May 2016); therefore S was experimentally started on an intermittent, every-3-day 6-IU dose. He was observed to demonstrate decreased appetite and steady weight loss when he was increased to a daily 6-IU dose. NAL, from Sun Pharmaceuticals (Dadra, India), was added after 10 weeks of intranasal OT treatment to mitigate his hedonic food-seeking. Studies on NAL’s effective impact on reducing appetite used doses ranging from 50 to 200 mg/d (13, 14); we selected a midrange dose of 100 mg/d.

Neuroimaging

Brain MR imaging 6 months after CP resection demonstrated no gross residual tumor. There was mild lateral and third ventriculomegaly. The posterior pituitary bright spot was absent, consistent with diabetes insipidus. Magnetic resonance imaging evaluation of hypothalamic injury using a validated system by Roth et al. (20) demonstrated evidence of injury to the floor of the third ventricle and bilateral anterior hypothalamus, including the region of the paraventricular nuclei and supraoptic nuclei. There was also evidence of at least unilateral injury to the medial and posterior hypothalamus, including the region of the arcuate nucleus; however, the mammillary bodies appeared intact. (Fig. 1).

Medications

At the outset of OT treatment, S’s panhypopituitarism symptoms were treated with full replacement doses of desmopressin, hydrocortisone, levothyroxine, liothyronine, and growth hormone. Additionally, S took fish oil for hyperlipidemia, and 6 mg/night melatonin and 5 mg/d dextroamphetamine for his disrupted circadian rhythm and daytime somnolence, respectively. Four months after starting OT treatment, S began receiving subcutaneous 24 mg/wk testosterone to induce puberty due to hypogonadotropic hypogonadism. Due to his poor response to 6 mg/night, S’s melatonin dose was lowered to 0.3 mg/night 7 months after starting OT.

Results

Initial 10-week OT treatment (phase 1)

On a 6 IU/d dose of intranasal OT, S began to steadily lose weight (Fig. 2). Thirty days before starting the therapeutic dose, S was 170 cm tall and weighed 77 kg; his BMI z score was 1.77 standard deviation score (SDS) (96th percentile). After 10 weeks of treatment, he was
171 cm tall and weighed 72.6 kg; he lost 4.4 kg, and his BMI $z$ score dropped to 1.49 SDS (93rd percentile). S also demonstrated noticeable qualitative changes in the areas of improved satiety (leaving food unfinished), decreased urgency to eat (tolerating longer intervals between snacks and meals), and overall decreased food preoccupation (talking less often about food, insisting less on being in the kitchen). Despite these improvements, when an opportunity arose to attain highly palatable foods (e.g., cookies and candy), he continued surreptitious food-seeking of these types of food. Increasing the dose of intranasal OT to 9 IU/d actually worsened his food-seeking behaviors; therefore, after 25 days, the dose was subsequently reduced back to 6 IU/d.

**Subsequent 38-week OT and NAL treatment (phase 2)**

After 10 weeks of intranasal OT and to curb his seeking of highly palatable foods, S was started on 100 mg/d NAL. Five months after beginning the 6 IU/d of intranasal OT and 100 mg/d of NAL, S’s BMI $z$ score dropped from 1.49 SDS (93rd percentile) to 1.31 SDS (90th percentile). We observed his continued improved satiety and decreased preoccupation with food; he was then granted partial unlocked-kitchen access to the refrigerator and one snack cabinet. After 6 weeks, his BMI $z$ score dropped further to 1.15 SDS (87th percentile), and S was granted access to a fully unlocked kitchen. During phase 2, he grew 6.4 cm and lost 2.9 kg, and his BMI $z$ score was 0.82 SDS (79th percentile) while living for 10 weeks with full kitchen access. At the study’s end, S was 177.4 cm tall and weighed 69.7 kg, and over the course of the entire study, S grew 7.4 cm and lost 7.3 kg. However, despite the reduction of weight and hyperphagia, S was still observed to engage in opportunistic hedonic food-seeking outside of the home.

To date, S has tolerated both treatments well with no discernible adverse effects. A common effect from OT is fluid retention because OT, like vasopressin, possesses antidiuretic properties. However, S did not retain extra fluids from the OT, and his desmopressin (hormone replacement for diabetes insipidus) dose has remained the same (4.0 mg/d), with his electrolytes staying within normal limits.

**Discussion**

This case demonstrates a unique and effective treatment of CP-related HO and hyperphagia by using OT and additional NAL. Whereas Daubenbäch et al. (21) found existing OT levels in postresection CP patients, the obesity, hyperphagia, and imaging evidence of damage to the bilateral paraventricular nucleus and supraoptic nucleus, where OT is normally produced (22), confirm S’s poorly functioning postresection oxytocinergic system.

OT has been shown to have anorexigenic effects in humans (23–25) and animals (26–28). The anorexigenic effects of exogenous OT treatment are thought to be multifactorial in nature. Although OT levels have been shown to be significantly increased in both plasma and cerebrospinal fluid after intranasal administration in humans (29) and nonhuman primates (30), there is a question about the possibility that intranasal OT may fail to penetrate the central nervous system (31). Another route of exogenous intranasal OT supplementation is likely mediated via OT receptors located in a variety of undamaged brain areas through vagal afferents terminating in the hindbrain nucleus of the solitary tract (32, 33) as well as in peripheral organs of the body (34), including the GI tract and nodose ganglion (35). Zhang et al. (36) found that peripheral OT activated hypothalamic OT neurons to release OT, whereas Morton et al. (37) demonstrated that the hindbrain nucleus of the solitary tract neurons is also activated by systemic OT. Carson et al. (38) administered OT into rats and found that it increased Fos expression in several regions, including in the OT-synthesizing neurons of the supraoptic nucleus and paraventricular nucleus of the hypothalamus. These studies all demonstrate that peripheral OT...
may in fact stimulate the activation of endogenous OT, therefore bypassing the need for peripheral OT to enter the central nervous system to have an effect on food intake.

As an intervention for obesity, OT has been shown to decrease hypothalamic activity in response to high-calorie visual food cues, reduce food consumption, and increase brown adipose tissue thermogenesis and energy expenditure in lean and/or diet-induced obese rodent models (32, 39, 40). According to Deblon et al. (41), white adipose tissue may also possibly be a target of intranasal OT.

Nascent clinical trials of OT suggest that intranasal OT acutely reduces food intake at meals, snack food consumption, reward-induced eating, and obesity (23–25, 42). We observed similar findings in the case of S, except that he continued to exhibit opportunistic food-seeking of highly palatable, sweet foods. Ott et al. (23) hypothesized that OT typically regulates non-homeostatic, reward-related energy intake via a combination of hypothalamic-pituitary-adrenal (HPA) axis activity and regulates the glucose response to food intake. Although S decreased his homeostatic hunger and hyperphagia, the continuation of impulsive hedonic food-seeking behaviors following OT and NAL therapy may be due to damage to other neuronal circuits of the brain reward system, including certain regions of the corticolimbic and mesolimbic structures (11) involved in highly palatable food-seeking behaviors.

Opioid receptor antagonists, such as NAL, can reduce the reinforcing values of food and food-related rewards (43). In a study of NAL’s effect on cerebrospinal...
fluid melanocortin peptides and cortisol levels in humans, Gordon et al. (44) found that agouti-related protein and cortisol stimulation by NAL may mitigate hypothalamic proopiomelanocortin-induced decrease in food intake. Cravings for both food and drugs are strongly linked; both hedonic food and drug seekers share a common disruption in dopaminergic pathways (45). In studies on recently abstinent alcoholics treated with NAL, elevated plasma concentrations of cortisol and adrenocorticotropic hormone and the plasma concentrations of cortisol correlated negatively with the level of alcohol craving (46, 47). These studies suggest that NAL’s effect on the release of food and alcohol craving might be related to its ability to activate the HPA axis and may be argued to explain NAL’s failure to deter hedonic food-seeking given S’s panhypopituitarism and nonintact HPA axis. Nevertheless, NAL may have potentiated the therapeutic effects of OT by stimulating the release of existing amounts of endogenous OT (21), however small.

This case report has several limitations. Although we observed S’s decreased urgency to eat and improved satiety, we were unable to attain quantified accurate measures and changes of calorie intake due to his superstitious hedonic food-seeking behavior. For this reason, we were forced to rely upon our qualitative observations of his food intake. Carbohydrate restriction also played a role in his BMI decrease, and future studies would benefit from having tighter controls over food intake. The role of NAL, whether adjunctive to OT or not, may be further tested by a longer study of OT without NAL. Additionally, the lack of dosing guidelines for these unique interventions brings to question whether treatment effects might have been optimized at different doses. Future studies should focus on longer treatment at various doses using standardized assessments for energy intake and expenditure and for eating behavior and hyperphagia assessment.

Conclusion

The successful and sustained reduction of weight and hyperphagia using OT and additional NAL was demonstrated in a boy with HO secondary to CP. The dearth of clinical trials using OT and NAL, the lack of effective treatment options, and the resultant poor quality of life for this population compels future research on this promising intervention for this difficult-to-treat obesity syndrome. Moreover, given the public health crisis posed by the explosive rates of worldwide obesity and its associated high morbidity, this well-tolerated and successful intervention on such a treatment-recalcitrant syndrome motivates further study on other more common forms of obesity.

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References


