Chronic oxytocin administration inhibits food intake, increases energy expenditure, and produces weight loss in fructose-fed obese rhesus monkeys

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Blevins JE, Graham JL, Morton GJ, Bales KL, Schwartz MW, Baskin DG, Havel PJ. Chronic oxytocin administration inhibits food intake, increases energy expenditure, and produces weight loss in fructose-fed obese rhesus monkeys. Am J Physiol Regul Integr Comp Physiol 308: R431–R438, 2015. First published December 24, 2014; doi:10.1152/ajpregu.00441.2014.—Despite compelling evidence that oxytocin (OT) is effective in reducing body weight (BW) in diet-induced obese (DIO) rodents, studies of the effects of OT in humans and rhesus monkeys have primarily focused on noninvasive behaviors. The goal of this study was to translate findings in DIO rodents to a preclinical translational model of DIO. We tested the hypothesis that increased OT signaling would reduce BW in DIO rhesus monkeys by inhibiting food intake and increasing energy expenditure (EE). Male DIO rhesus monkeys from the California National Primate Research Center were adapted to a 12-h fast and maintained on chow and a daily 15% fructose-sweetened beverage intake by 18 P/H11003 and maintained on chow and a daily 15% fructose-sweetened beverage over 1 wk. We subsequently identified doses of OT (0.2 and 0.4 mg/kg) that reduced food intake and BW in the absence of nausea or diarrhea. Chronic administration of OT for 4 wk (0.2 mg/kg for 2 wk; 0.4 mg/kg for 2 wk) reduced BW relative to vehicle by 3.3 ± 0.4% (=0.6 kg; P < 0.05). Moreover, the low dose of OT suppressed 12-h chow intake by 26 ± 7% (P < 0.05). The higher dose of OT reduced 12-h chow intake by 27 ± 5% (P < 0.05) and 8-h fructose-sweetened beverage intake by 18 ± 8% (P < 0.05). OT increased EE during the dark cycle by 14 ± 3% (P < 0.05) and was associated with elevations of free fatty acids and glycerol and reductions in triglycerides suggesting increased lipolysis. Together, these data suggest that OT reduces BW in DIO rhesus monkeys through decreased food intake as well as increased EE and lipolysis.

istration of OT recapitulates the effects of central administration of OT to reduce BW and reduce BW gain in DIO rodents (1, 22, 40, 44, 71, 72). Similar to its effects on BW, OT also inhibits food intake in DIO (22, 40, 45, 71, 72) and genetically obese rodent models (1, 39, 41, 45). In addition to reducing intake of a low-fat/high-carbohydrate diets, including standard rodent chow (22, 40, 45, 71), OT also reduces consumption of sucrose (47) as well as high-fat diets (45, 71, 72). Conversely, impairments of OT signaling are associated with increased consumption of carbohydrates, including sucrose (2, 30, 47, 52), fructose (30), and glucose (30), as well as fat (71, 72), implicating a potential physiological role for OT to limit consumption of both simple sugars and fat.

Recent studies indicate that in addition to suppressing food intake, OT may also reduce BW in rodents by increasing energy expenditure (EE). Reductions of OT signaling are linked to obesity as well as decreases of EE (15, 35, 62, 67, 72), including impairments in sympathetic nervous system activity, thermogenesis by brown adipose tissue (BAT) (15, 35, 62), and oxygen consumption (67, 72) in the absence of increases of food intake (2, 15, 62, 67, 68) in mice. On the other hand, acute administration of OT into the CNS produces short-term increases of EE (48, 71, 72) in addition to heart rate (32, 70) and body temperature (70) in rodents. When administered by chronic subcutaneous infusion to DIO rats, OT also reduces BW at doses that are ineffective at reducing food intake (22). In cases where chronic subcutaneous OT treatment inhibits both food intake and BW, its ability to reduce BW is maintained for 9 days after treatment has ended (40) or food intake has returned to baseline pretreatment levels (40). These findings are consistent with data that show that BW loss attributed to systemic treatment with OT exceeds that of pair-fed control animals (22, 45). OT also activates sympathetic preganglionic neurons (6), including the stellate ganglia (5). With well-characterized polysynaptic projections to BAT (50), stellate ganglia (34), and the spinal cord (55), these findings suggest that OT may have an important role in regulating sympathetic nervous system activity.

However, despite compelling evidence that OT has important effects on energy balance and BW in rodents, studies in humans and nonhuman primates (NHPs) have primarily focused on the role of OT in mood, trust, and pair bonding. The goal of this study was therefore to establish a proof of principle that systemic OT treatment is effective at inducing weight loss in a NHP model of DIO. We determined the extent to which chronic administration of OT induces long-term BW loss in DIO rhesus monkeys and assessed whether these effects on BW loss were maintained following cessation of treatment. We further examined whether this OT-induced BW loss is mediated by reductions in food intake as well as increases of EE and/or lipolysis.

METHODS

Animals

Adult male rhesus monkeys (N = 5) (age: 10–18 yr, BW: 17.5 ± 1.1 kg) (37.9 ± 1.9% fat) from the California National Primate Research Center (CNPRC) Primate Resource were maintained at the CNPRC at the University of California, Davis. All animals were housed individually in a temperature-controlled room under a 12:12-h light-dark cycle (lights off at 6 PM; lights on at 6 AM). Animals had ad libitum access to water throughout the study and were adapted to a daily 12-h fast (during dark phase from 6 PM to 6 AM) with the exception of when the animals were placed into indirect calorimetry cages for their EE measurements at baseline and at the conclusion of week 4 of the treatment period. The research protocols were approved both by the Institutional Animal Care and Use Committees of the University of California, Davis and conducted in accordance with the Department of Agriculture Animal Welfare Act and National Institutes of Health Guidelines for the Care and Use of Animals.

Injections and Drug Preparation

Fresh solutions of OT acetate salt (American Peptides, Sunnyvale, CA) were prepared on each day of the experiment within 30–45 min of administration. OT was solubilized in sterile water and diluted with sterile saline. Both vehicle and OT were filtered (0.22 μm filter, EMD Millipore, Billerica, MA) before administration. Vehicle injections (0.1 ml/kg injection volume) were administered subcutaneously 2× daily between 6:45 AM and 7:00 AM and 2:45 PM and 3:00 PM during week 1 (Fig. 1). OT injections were administered in identical fashion during weeks 2–5 (0.2 mg/kg) and weeks 4–5 (0.4 mg/kg). A pilot study was undertaken before the start of the experiment to confirm effective dosing based on an acute decrease of food intake. These animals were the same as those used in the chronic administration study. Each animal served as its own control and received 1× daily injections of vehicle or OT (0.04, 0.2 mg/kg; 0.1 ml/kg injection volume) in randomized fashion between 6:45 AM and 7:00 AM at 48-h intervals.

Diet and Energy Intake Measurements

Animals were maintained on a standard monkey chow diet (High Protein Monkey Diet Junimo 5047, Advance Protocol Old World Primate; LabDiet, St. Louis, MO), which consists of 11% kcal from fat, 30% kcal from protein, and 59% kcal from carbohydrate. Fresh chow was given to the animals at 7 AM and was replaced daily at 3 PM. In addition, all animals were provided 1× daily with a 15% fructose-sweetened beverage flavored with unsweetened Kool-Aid (Kraft Foods Group, Northfield, IL) at 7 AM. Cumulative energy intake (chow diet + sweetened beverage) was measured 2× daily at 3 PM and 7 PM using previously established methods in the CNPRC (12). Cumulative 8- and 12-h food intake data were averaged across the 1-wk vehicle treatment period, 2-wk OT treatment periods, and the first 2 wk of the washout period. During the pilot study cumulative food intake was measured at 0.5, 1, 8, and 12 h following access to

<table>
<thead>
<tr>
<th>Week</th>
<th>VEH (saline)</th>
<th>OT (0.2mg/kg)</th>
<th>OT (0.4mg/kg)</th>
<th>Washout</th>
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Fig. 1. Experimental paradigm for chronic administration of oxytocin (OT) or vehicle into diet-induced obese (DIO) nonhuman primates (NHPs). BW, body weight; SQ, subcutaneous.
food at 7:00 AM. Cages were inspected daily for signs of nausea or diarrhea.

**Indirect Calorimetry**

EE was assessed \(2 \times (1 \times \text{at baseline and } 1 \times \text{at conclusion of week } 4 \text{ treatment})\) over 24-h periods using indirect calorimetry (\(\text{O}_2, \text{CO}_2\)) in metabolic chambers at the CNPRC (12) Exposure Facility. The indirect calorimetry measurements were completed in two airtight 32" height \(\times 27" \text{ depth} \times 24" \text{ width} \) chambers at 30-min intervals (12). EE was calculated using the Weir equation: kcal/min

\[
\text{EE} = \frac{\text{V}_{\text{O}2} - \text{V}_{\text{CO}2}}{0.793} \times 4.893
\]

To control for the influence of body size variation on total EE (13), group comparisons involving this outcome were analyzed following normalization to body weight and lean body mass. Monkeys were placed into the chambers between 7 AM and 9 AM and were given ad libitum access to the fructose-sweetened beverage, standard monkey chow, and water, and remained in the chambers until 6 AM. The area under the curve (AUC) was calculated using the trapezoidal method.

**Body weight.** BW was determined \(1 \times \text{weekly at the end of baseline, vehicle treatment, OT treatment and weeks } 1-3 \text{ and } 7 \text{ of the washout period.}\)

**Plasma measurements.** Fasting blood samples (15 ml) were drawn into EDTA Vacutainer tubes \(1 \times \text{weekly between } 6:15 \text{ AM and } 6:30 \text{ AM immediately before administration of vehicle or OT.}\) Samples were collected at the conclusion of baseline, vehicle, or OT treatment from a cephalic vein in conscious monkeys using the arm-pull technique after an overnight fast.

**Plasma Assays**

Whole blood was centrifuged at 6,000 rpm for 15 min at 4°C, plasma was removed, and was aliquoted and stored at \(-80^\circ\text{C}\) for subsequent analysis.

**Adiponectin, Insulin, Leptin, and OT**

Plasma adiponectin, insulin, and leptin were measured by radioimmunoassay (RIA, EMD Millipore, Billerica, MA). These assay procedures have been validated for rhesus monkeys using already established procedures (12). The intra-assay coefficient of variation (CV) for adiponectin, insulin, and leptin were 5.4, 6.5, and 3.5%, respectively. The limits of detectability for the RIAs are as follows: adiponectin (0.8–100 ng/ml), insulin (2.7–200 U/ml), and leptin (1–100 ng/ml). Plasma OT levels were determined by ELISA (ENZO Life Sciences, Farmingdale, NY).

The intra-assay CV for OT was 4.5% and the limit of detectability was 15–1,000 pg/ml.

**Glucose, Lipid, and Lipoproteins**

Glucose, triglycerides (TG), total cholesterol, high-density lipoprotein (HDL), direct low-density lipoprotein (LDL), apolipoprotein A1 (ApoA1), and apolipoprotein C3 (ApoC3) concentrations were measured using an enzymatic-based Polychem Chemistry Analyzer (MedTest DX, Canton, MI). Free fatty acids (FFAs) were measured using an enzymatic-based kit (Wako Chemicals, Richmond, VA). These assay procedures have been validated for rhesus monkeys (12). The intra-assay CV for glucose, total cholesterol, HDL, LDL, ApoA1, ApoC3, FFAs, and TGs were 0.6, 2.9, 2.0, 0.5, 2.4, 0.7, 2.2, and 3.5%, respectively.

**Statistics**

All results are expressed as means ± SE. Comparisons between treatments were made using a one-way repeated measures ANOVA with a Fisher's least significant difference post hoc test. Analyses were performed using the statistical program SYSTAT (Systat Software, Point Richmond, CA). To control for the influence of body size variation on total EE (13), group comparisons involving this outcome were adjusted for total body mass and lean mass using the statistical program GraphPad Prism (GraphPad Software, La Jolla, CA). Differences were considered significant at \(P < 0.05\).

**RESULTS**

**BW Gain After Exposure to Fructose-Sweetened Beverage**

Animals were maintained on 500 ml/day of a 15% fructose-sweetened beverage and ad libitum access to their usual standard chow diet for 10.8 ± 0.1 mo before study onset where animals weighed 15.0 ± 1.2 kg at baseline and 17.5 ± 1.1 kg (\(\text{ABW} = +2.5 \pm 0.7 \text{ kg}\) after exposure to the intervention diet \((P < 0.05)\). We have previously reported that supplementation of an ad libitum chow diet with 15% fructose-sweetened beverages over 6- and 12-mo periods result in similar increases in BW at 6 and 12 mo (11, 12). These differences were associated with 29% and 35% increases of fat mass at 6 and 12 mo, respectively (12).

**Effects of OT on Body Weight**

The initial goal of this study was to determine whether chronic OT treatment would elicit BW loss in a more translational NHP model of DIO. Overall, there was a significant main effect of OT to reduce BW [\(F(4,16) = 15.760, P < 0.05\) ]. OT elicited BW loss compared with vehicle treatment after 2 \((-0.41 \pm 0.09 \text{ kg})\), 3 \((-0.41 \pm 0.08 \text{ kg})\), and 4 wk \((-0.58 \pm 0.04 \text{ kg})\) of treatment (Fig. 2A; \(P < 0.05\)). At the end of vehicle and OT treatment, animals weighed 17.7 ± 1.1 kg and 17.1 ± 1.10 kg, respectively \((P < 0.05)\). Chronic OT treatment elicited BW loss in all five animals relative to vehicle treatment. These data are the first to demonstrate that chronic OT induces BW loss in a NHP model of DIO.

To determine whether the BW loss resulting from OT administration extended beyond cessation of treatment, BW was determined during a washout period out to 7 wk posttreatment. There was a significant main effect of OT to maintain BW loss relative to vehicle treatment throughout the washout period [\(F(4,16) = 14.112, P < 0.05\) ]. Weight loss remained below that following vehicle treatment during week 1 \((P < 0.05)\), week 2 \((P < 0.05)\), and week 7 \((P = 0.056)\) of the washout period. Animals did not begin to gain significant BW relative to the end of the OT treatment until week 3 of the washout period (Fig. 2B; \(P < 0.05\)).

**Effects of OT on Consumption of Chow and Fructose-Sweetened Beverage**

To determine whether the effects of OT to elicit weight loss is due, in part, to reductions of energy intake from chow and fructose, cumulative 8- and 12-h food intake was measured throughout the vehicle and OT treatment. Whereas there was no significant main effect of OT to reduce chow consumption at 8 h [\(F(2,8) = 3.602, P = 0.077\)] , there was a significant main effect of OT to reduce chow consumption at 12 h [\(F(2,8) = 11.816, P < 0.05\) ]. Specifically, we found that the low dose of OT \((0.2 \text{ mg/kg})\) suppressed 12-h chow intake by 26 ± 7% (Fig. 3A; \(P < 0.05\)). The higher dose of OT \((0.4 \text{ mg/kg})\) suppressed 8- and 12-h chow intake by 13 ± 9 and 27 ± 5% \((P < 0.05)\), respectively.

There was no significant main effect of OT to reduce 8-h fructose-sweetened beverage intake (Kool-Aid) [\(F(2,8) = 1.321, P = 0.288\) ].
While the lower dose of OT (0.2 mg/kg) failed to significantly reduce fructose-sweetened beverage intake at 8 h, the higher dose of OT (0.4 mg/kg) reduced 8-h fructose-sweetened beverage intake by 18% (Fig. 3B; P = 0.05). Importantly, there were no signs of nausea or diarrhea following administration of OT at either dose upon daily inspection. Moreover, we found that there were no differences in 8- or 12-h chow (Fig. 3A) or Kool-Aid (Fig. 3B) consumption in animals treated with OT treatment (0.4 mg/kg) relative to the same animals 2-wk after the washout period (P = NS). These findings suggest that the effects of OT to reduce food intake are prolonged, and second, prevent the rebound hyperphagia that is characteristic following weight loss.

Effects of OT on Energy Expenditure

To determine whether increased EE may also contribute to the effects of OT to produce weight loss, we measured EE using indirect calorimetry (normalized to BW) at both baseline and during the last week of treatment. Our findings show that there was a main effect of OT to increase total EE [F(1,4) = 18.060, P < 0.05]. This effect of systemic OT to increase EE was primarily due to an increase in EE during the dark cycle [F(1,4) = 35.068, P < 0.05] (Fig. 4A) with a tendency to increase EE during the light cycle [F(1,4) = 4.992, P = 0.089]. Specifically, systemic OT increased EE by 14.4 ± 3.0 and 9.2 ± 1.8% during the 12-h dark cycle and entire 24-h period, respectively (Fig. 4B). OT did not significantly stimulate EE during the 9-h light cycle measurements (3.8 ± 1.7%; P = 0.09). Similar results were also observed when the data were normalized to lean body mass.

**Plasma Measurements After OT Treatment**

OT treatment resulted in increased plasma OT, FFAs, and glycerol (P = 0.05) concentrations, in addition to reductions of plasma glucose and TG concentrations, and modest decreases of total and LDL cholesterol, and ApoC3 (P < 0.05) (Table 1).

**DISCUSSION**

The goal of this study was to translate the previous findings in DIO rodent models to a preclinical translational NHP model of DIO. Here we show for the first time that chronic administration of OT is sufficient to elicit long-term weight loss in fructose-fed DIO rhesus monkeys. Furthermore, we observed that this weight loss remained below that of vehicle treatment for 7 wk into the washout period, and significant weight regain did not begin until week 3 of the washout period. In addition, we determined that the ability of OT to elicit weight loss appears to be attributed, in part, to reductions in consumption...
of both chow and fructose-sweetened beverage in the absence of nausea or diarrhea. We also identified that chronic systemic administration of OT increases EE in addition to increasing FFAs and reducing TGs as well as total cholesterol. Together, these findings provide evidence that chronic systemic OT effectively produces long-term reductions in BW in DIO rhesus monkeys through mechanisms that may include reductions of food intake, in addition to increases of EE and possibly increased lipolysis.

These findings are consistent with data from studies in rodents reporting that administration of OT results in BW loss or decreased BW gain. Chronic administration of OT over a period between 7 and 42 days is sufficient to reduce either BW or BW gain in DIO mice and rats (22, 40, 44, 71, 72) as well as genetically obese mice (1). Of particular interest in our study is the observation that BW loss persisted below that of vehicle control treatment out to 7 wk during the washout period, and animals did not regain significant BW until week 3 of the washout period. These prolonged effects are consistent with other reports in obese NHP treated with adipotide (7), a melanocortin 4 agonist BIM-22493 (38), or fibrolast growth factor-21 (37, 64), and appear to be mediated, in part, by reductions of food intake that persisted for the initial 2 wk of the washout period. Similarly, Maejima and colleagues (40) showed that BW gain continued to remain below that of vehicle controls for 9 days following cessation of OT treatment in DIO mice. In addition, the effects of OT on exploratory and antiaggressive behavior persist for at least 7 days following cessation of treatment in male rats (14). Recent studies show that acute systemic administration of OT is capable of activating PVN OT neurons (16, 31) and stimulating the release of OT in the PVN in a rodent model (72). These self-stimulatory properties (22) in addition to its prolonged bioavailability of OT in the central nervous system (CNS) are thought to contribute, in part, to its positive effects on prosocial behavior (36) and may also contribute to the prolonged effects of OT on BW loss following cessation of treatment (40).

Our findings indicate that OT reduced the intake of both standard monkey chow and a fructose-sweetened beverage and may point to a potential role of OT to limit consumption of carbohydrates or sweets in primates. These findings are consistent with those showing that exogenous administration of OT reduces sucrose intake in rodents (47) as well as consumption of chocolate cookies in humans (53). Based on recent data it appears that an important physiological role of OT is to limit intake of sucrose (2, 30, 47, 52), in addition to other simple sugars [fructose (30) and glucose (30)]. Reductions of endogenous OT signaling also stimulate intake of rodent chow, which contains up to 58% energy (kcal) from carbohydrates (3, 47)

Table 1. Plasma measurements after daily subcutaneous administration of OT or vehicle

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<tr>
<th></th>
<th>Baseline</th>
<th>Vehicle</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
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<tr>
<td>Leptin, ng/ml</td>
<td>62.3 ± 7.5</td>
<td>65.9 ± 7.2</td>
<td>69 ± 7.3³</td>
<td>61.5 ± 4.8</td>
<td>60.7 ± 6.0</td>
<td>58.9 ± 7.7</td>
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<tr>
<td>Insulin, µU/ml</td>
<td>275 ± 51</td>
<td>243 ± 33</td>
<td>254 ± 56</td>
<td>259 ± 36</td>
<td>259 ± 47</td>
<td>276 ± 61</td>
</tr>
<tr>
<td>Adiponectin, µg/ml</td>
<td>5.9 ± 1.3</td>
<td>5.9 ± 1.5</td>
<td>5.7 ± 1.3</td>
<td>4.7 ± 1.4</td>
<td>5.3 ± 2.0</td>
<td>5.0 ± 2.2</td>
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<tr>
<td>Glucose, mg/dl</td>
<td>124 ± 30</td>
<td>130 ± 31</td>
<td>120 ± 27</td>
<td>115 ± 26</td>
<td>114 ± 20</td>
<td>100 ± 14*</td>
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<td>FFA, meq/l</td>
<td>0.40 ± 0.02</td>
<td>0.38 ± 0.05</td>
<td>0.42 ± 0.06</td>
<td>0.46 ± 0.06*</td>
<td>0.52 ± 0.06*</td>
<td>0.46 ± 0.02*</td>
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<tr>
<td>Glycerol, mg/dl</td>
<td>0.64 ± 0.19</td>
<td>0.66 ± 0.25</td>
<td>0.64 ± 0.23</td>
<td>0.53 ± 0.17</td>
<td>0.79 ± 0.17</td>
<td>0.83 ± 0.14+</td>
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<td>TG, mg/dl</td>
<td>470 ± 234</td>
<td>406 ± 148</td>
<td>353 ± 180</td>
<td>463 ± 248</td>
<td>360 ± 140</td>
<td>279 ± 95**</td>
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<td>Total cholesterol, mg/dl</td>
<td>174 ± 17</td>
<td>162 ± 9</td>
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<td>167 ± 18</td>
<td>156 ± 12‡</td>
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<td>LDL, mg/dl</td>
<td>60 ± 4</td>
<td>53 ± 3</td>
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<td>59 ± 5</td>
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<td>HDL, mg/dl</td>
<td>63 ± 11</td>
<td>56 ± 11</td>
<td>58 ± 12</td>
<td>59 ± 11</td>
<td>55 ± 11*</td>
<td>55 ± 10*</td>
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<td>ApoC3, mg/dl</td>
<td>10 ± 2</td>
<td>9 ± 2</td>
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<td>8 ± 1*</td>
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<td>ApoA1, mg/dl</td>
<td>114 ± 15</td>
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<td>109 ± 14</td>
<td>112 ± 16</td>
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<td>115 ± 14</td>
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<td>OT, pg/ml</td>
<td>2,942 ± 265</td>
<td>2,594 ± 202</td>
<td>2,701 ± 160</td>
<td>3,259 ± 202</td>
<td>3,704 ± 237*</td>
<td>4,250 ± 570*</td>
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Values are means ± SE; n = 5 animals/group. FFA, free fatty acid; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OT, oxytocin. *P < 0.05 vs. baseline; †P = 0.05 vs. baseline; ‡0.05<P < 0.1 vs. baseline; §P = 0.1 vs. baseline.
4, 8, 51, 71, 72). While additional studies to determine whether OT impacts macronutrient preference in NHPs will be informative, together, these findings build on existing rodent data and suggest that the effects of OT to limit consumption of carbohydrates may extend to primates.

The effects of OT to increase EE also appear to contribute toward its effects to reduce BW, although the site(s) of OT action in the CNS underlying these effects in rhesus monkeys remain to be identified. Recent findings show that direct administration of OT into the ventromedial hypothalamus (VMH) increases short-term EE in rats (48). Moreover, adeno-associated viral recovery of OTRs into the VMH/dorsomedial hypothalamus (DMH) of OTR-deficient mice restored impairments in cold-induced thermogenesis (35), providing further evidence that OTRs in the DMH/VMH are linked to the regulation of EE. While systemic OT increases the induction of Fos (a marker of neuronal activation) in the VMH in mice (72) and OTRs are expressed in the VMH of rhesus monkeys (9, 24), it remains to be determined whether systemic OT is capable of reaching OTRs in the DMH or VMH in sufficient concentrations to stimulate EE in rhesus monkeys. In addition to potential actions in either the VMH or DMH, OT could also increase sympathetic nervous system activity through polysynaptic projections from premotor neurons in the NTS (that potentially express OTRs) to BAT (34, 50, 55). Future studies will be required to address the extent to which these effects are mediated through direct actions in the VMH, NTS or elsewhere in the CNS.

Based on our findings that OT increased FFAs and tended to increase plasma glycerol concentrations suggest that OT may also reduce BW, in part, by increasing lipolysis. This could occur through a direct effect on adipocytes (27, 46, 56, 63). In vitro data from show that incubation of cultured 3T3-L1 adipocytes with OT increases enzymes associated with lipolysis (22) and results in increased glycerol release (22). In addition, chronic OT treatment in vivo results in reductions in fat mass (22, 40, 72), particularly adipocyte area from both the mesenteric and epididymal fat depots (40). Consistent with these findings, in vivo data from rodents with global loss in OT signaling report increases of abdominal fat deposition (15, 62) and increases of perirenal, mesenteric, and epididymal fat depot weights relative to wild-type littermate controls (62). Similarly, selective ablation of OT neurons in the PVN and SON (67) is associated with increases of body fat. Together, these recent studies unveil potential mechanisms whereby the OT reduces body fat through separate or combined effects to reduce food intake, promote lipolysis, and increase EE.

**Perspectives and Significance**

Chronic consumption of a high-fructose diet produces weight gain and metabolic perturbations (insulin resistance and dyslipidemia) associated with the metabolic syndrome and Type 2 Diabetes Mellitus (T2DM) in rhesus monkeys (12). With the disturbing rise in obesity in recent years attributed, in part, to increased sugar intake, there is urgent need to translate the promising results reported in DIO rodent models to examine the extent to which OT pharmacotherapy reduces BW in DIO primates. Given the need for new therapeutic strategies for the treatment of obesity, it is surprising that, up to now, there has yet to be a single clinical trial performed to systemically investigate the effects of chronic OT administration on food intake and BW in DIO NHPs or in obese humans. While one preliminary study by Zhang and colleagues (73) demonstrated that chronic intranasal OT reduced BW over an 8-wk period in prediabetic obese humans, they did not examine the extent to which these effects may be attributed to reductions in food intake as well as increases in EE and/or lipolysis. Here we provide the first key evidence that chronic administration of OT is a potential therapy that can produce long-term reductions in BW in a NHP model of diet-induced obesity through mechanisms that may involve reductions of energy intake as well as increases of EE and lipolysis. While this percent weight loss is less than that achieved in long-term (≥1 year) studies in humans treated with FDA-approved drugs such as Qsymia (phentermine + topiramate) (∼10.9% of initial BW), it is similar in magnitude to BW loss following either orlistat (∼3.1% of initial BW) or lorcaserin (Belviq; ∼3.2% initial BW) (7, 28). It should be stressed also that in most human obesity studies, subjects are placed on a “healthy” diet intended to enhance weight loss (often in conjunction with increased physical activity and other “lifestyle” interventions), whereas in our study, subjects were maintained on the same obesogenic diet throughout the study. Last, the amount of BW loss we observed is similar to what Kievet and colleagues (13) reported following chronic administration of a selective melanocortin receptor 4 agonist BIM-22493 over 4 wk (∼1 kg) in DIO rhesus monkeys maintained on a high-fat diet. Together, these findings provide key translational data to support future larger scale and longitudinal studies that examine the effects of chronic administration of OT on weight loss, macronutrient preference, and feeding reward in both male and female obese nonhuman primates, as well as in clinical studies in humans.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


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