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Opposite effects of oxytocin on water intake induced by hypertonic NaCl or polyethylene glycol administration

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HIGHLIGHTS

- Oxytocin increases urine volume and natriuresis after hypertonic NaCl administration.
- Oxytocin (OT) reduces the water intake induced by hypertonic NaCl administration.
- In contrast, OT reduces urine volume after polyethylene glycol (PEG) treatment.
- OT increases the water intake induced by PEG administration.
- This study suggests a differential regulatory effect of OT during states of intra- and extracellular thirst.

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ABSTRACT

Oxytocin (OT), a neurohormone, has been related to natriuretic and diuretic effects and also to water intake and sodium appetite. The objective of the present study was to determine the effect of subcutaneous OT administration on water intake and urine-related measures induced by the administration of hypertonic NaCl (experiment 1) or polyethylene glycol (PEG) (experiment 2). Experiment 1 showed that OT administration increases the urine volume, urinary sodium concentration, and natriuresis and reduces the water intake, water and sodium balances, and estimated plasma sodium concentration induced by hypertonic NaCl administration. Conversely, experiment 2 showed that OT administration increases the water intake and the antidiuretic response induced by PEG administration. These results show that the opposite effects of OT on the water intake induced by hypertonic NaCl or PEG administration are accompanied by differential regulatory effects, enhancing a natriuretic response in the first experiment and generating an antidiuretic reaction in the second experiment. This study suggests a differential regulatory effect of OT during states of intra- and extracellular thirst.

1. Introduction

Water intake is a regulatory behavior that can be induced by hydromineral imbalances, particularly states of hyperosmolality or hypovolemia [2,17,18,40,51,52,55,62,75,84]. In general, hyperosmolar disturbances are experimentally produced by the administration of osmotically effective hypertonic solutions that do not cross the cell membrane. After hypertonic NaCl administration, water is drawn from the cells by osmosis, inducing water intake, antidiuresis, and urinary sodium excretion [18,24,50,52,75]. For their part, hypovolemic states can be generated by the intraperitoneal [23] or subcutaneous [73] administration of colloid substances such as polyethylene glycol (PEG). This dipsogenic agent reduces levels of extracellular fluid (largely water and sodium), diminishes urine and sodium excretion, and promotes delayed sodium appetite in the absence of changes in arterial blood pressure [7,52,61,64–66,70]. Hence, water intake appears to be a sodium-related behavior in both hyperosmolality and PEG-induced hypovolemic conditions and is therefore affected by the intake and excretion of mineral salts [39,84].

Oxytocin (OT) is a neuropeptide released into the brain by the parvocellular cells of the paraventricular (PVT) nucleus and into the bloodstream by the supraoptic and magnocellular component of PVT nuclei [12,45,53]. Various studies have related the brain action of OT to the suppression of sodium appetite [14,16,77]. However, the presence of OT in the bloodstream does not appear to be involved in the inhibition of this intake behavior [44]. In fact, it was unexpectedly observed that the systemic administration of OT increased the intake of hypertonic NaCl and water after PEG administration and that this effect was blocked by pre-treatment with oxytocinergic antagonists [77]. Given that this effect of OT on drinking behavior was paralleled by augmented renal excretion of sodium (natriuresis), it has been suggested that OT may have enhanced the volemic effect of PEG and therefore sodium appetite and water intake [26,69,77]. This possibility is compatible

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with the presence of OT kidney receptors [18,30,42,53,84] and with the natriuretic effects of OT administration [10,18,20,30,33,45,53,68,82].

Studies in our laboratory on OT and its relation to hydro-mineral regulatory behavior found that its effect on water intake and sodium appetite was determined by the intake and excretion of sodium. Thus, the increase in water [10] and hypertonic NaCl [11] intake observed in the food-deprived but not ad lib-fed animals treated with OT was always preceded by an increase in sodium and urine excretion. OT also increased the water intake of animals fed ad lib on a low sodium-diet [10]. Conversely, the polyuric and polydipsic effects of OT were reduced in a dose-dependent manner by the administration of hypertonic NaCl [8].

With this background, the present study was designed to determine whether the subcutaneous (s.c.) administration of OT reduces the water intake induced by hypertonic NaCl (experiment 1) and increases the water intake induced by PEG (experiment 2). These hypothetical opposite regulatory effects of OT on water intake are examined in terms of the hydro-mineral balance, particularly with respect to the urine and sodium excretion and water and sodium balance of animals during the experiments.

2. Materials and methods

2.1. Subjects

Male Wistar rats weighing 250–320 g from a breeding colony at the University of Granada were randomly assigned to two groups in experiment 1 and five groups in experiment 2. The animals were housed in individual cages with free access to water and food unless otherwise indicated. The room was maintained under a 12/12 h light/dark cycle (lights on 08:00 h) and at 21–23 °C. The use and handling of the animals followed the guidelines established by the European Union Directive 2010/63/EU and by the Spanish Law (53/2013). All efforts were made to minimize animal suffering and the number of animals used.

2.2. Drugs

OT (22 μg/ml in distilled water [DW]; Iven, Madrid, Spain) was s.c. injected at 1.6 ml/Kg body weight. DW (Serra Pamies, Tarragona, Spain) was s.c. injected at a dose of 1.6 ml/Kg body weight. NaCl (0.5 *M*; Acros Organic, New Jersey, USA) was intraperitoneally (i.p.) injected at 6.6 ml/Kg body weight. PEG (Polyethylene glycol, 20,000 *M*, Merck, Darmstad, Germany) was dissolved in saline solution (30%) and i.p. injected at 12.5 ml/Kg body weight. Ketamine (Ketolar, 50 mg/ml DW; Parke-Davis, Madrid, Spain) was intramuscularly (i.m.) injected at 75 mg/Kg body weight, inducing a mild anesthesia to facilitate the PEG injection given its high density.

The selection of doses was based on previous studies that demonstrated the natriuretic effect of OT [10] and the dipsogenic effects of hypertonic NaCl [8] and PEG [29,73].

2.3. Experimental procedure

2.3.1. Experiment 1

The animals were maintained in metabolic cages (3701MO-000; Tecniplast, Milan, Italy) with ad lib water and a standard diet (Harlan Global diet; Milan, Italy) for three days before the experiment (baseline). The water and food intake and body weight of each animal were recorded daily at 09.00 h. After the recording on day 3, water and food were removed from the cage. At 10.00 h, a graduated burette with water was offered, recording the amount of water consumed after 2 h. At 12.00 h, food and water were placed in the cage.

After the recording at 09.00 h on day 4, water and food were again removed from the cage and the animals were i.p. injected with hypertonic NaCl as described above. After a 30-min interval, OT was administered to one group of animals (NaCl/OT group, n = 7) and DW to another group (NaCl/DW group, n = 7). At 12.00 h, the amount of water consumed was recorded.

Urine samples were obtained for 3 h (from 09.00 to 12.00 h) on day 3 (before hypertonic NaCl administration) and on day 4 (after hypertonic NaCl administration). Urine sodium and potassium concentrations (in mEq/ml) were measured with an Ilyte analyzer (Instrumentation Laboratory, Barcelona, Spain) and used in combination with the urine volume data to calculate the excretion of sodium (natriuresis) and potassium (kaliuresis) in mEq. Fig. 1 depicts the timeline of the experimental procedures.

2.3.2. Experiment 2

The procedure as applied in other studies [29,73] usually offers animals a low sodium diet for 2–4 days before the experiments.

In the present experiment (Fig. 2), animals received water and standard chow ad lib (Harlan Global diet; Milan, Italy) for three days before habituation to water and food deprivation between 09.00 h and 18.00 h from day 4 onwards. After the 9-h deprivation period, they were offered water at 18:00 via a graduated burette to measure their water intake at 15, 30, and 120 min. From 20.00 h, food was available ad libitum: standard chow on days 4–6 (Harlan Global diet; Milan, Italy) and a low-sodium diet on days 7–9 (dextrin tablets with 0.02% sodium, Santiveri, Barcelona, Spain). Water and food intake and body weight were recorded on all days at 9:00 h. On day 10, after removing the water and food at 9:00, the animals were injected with ketamine and then, after a 10-min interval, with PEG and OT (PEG/OT group, n = 12) or DW (PEG/DW group, n = 12). PEG was injected using an 18-gauge hypodermic needle. Three additional control groups were included, following the same procedure, which were injected solely with OT (OT group, n = 7), DW (DW group, n = 7), or ketamine (n = 6) to verify the effect of each compound on water intake and to confirm the dipsogenic effects of the PEG administered in the PEG/DW group.

As on previous days, water was introduced at 18.00 h and the intake was measured at 15, 30, and 120 min, time intervals that are known to be adequate for detecting the dipsogenic effects of PEG [23,50]. Finally, from 20.00 h on day 10 until 09.00 h on day 11, groups treated with PEG remained in the metabolic cages with availability of water but not food.

Thus, the animals were placed in metabolic cages (3701MO-000; Tecniplast, Milan, Italy) from 09.00 to 20.00 h on days 7–10 and from 20.00 on day 10 to 09.00 on day 11. Urinary sodium and potassium concentrations (mEq/ml) were measured using an Ilyte analyzer (Instrumentation Laboratory, Barcelona, Spain), and the excretion of sodium (natriuresis) and potassium (kaliuresis) was calculated in mEq. Fig. 2 depicts the timeline of the experimental procedures.

2.4. Statistical analysis

The ANOVA module of STATISTICA software (StatSoft, Inc., Tulsa, OK, USA) was used for the data analyses. Baseline and experimental water intake, urine volume, urinary sodium and potassium concentrations, natriuresis and kaliuresis, water and sodium balances, and estimated plasma sodium concentration were analyzed by means of ANOVAs for OT and DW groups of experiment 1 and for PEG/DW, PEG/OT, OT, ketamine and DW groups of experiment 2. Plasma sodium concentration was estimated by using the following formula [73]: $1000 \times [(0.150)\ (0.69)\ (BW) + \text{sodium "balance"}] / [(0.69)\ (BW) + \text{water "balance"}]$, where BW was the body weight (in grams) of the animal at the time of testing, sodium "balance" (in mEq) was computed as the difference between injected sodium and sodium loss in urine, and water "balance" (in ml) was computed as water intake/injected *minus* urine volume. Significant effects were analyzed by means of a *post hoc* Tukey test. All data were expressed as means ± standard error of the mean (SEM) and statistical significance was set at the 5% level.

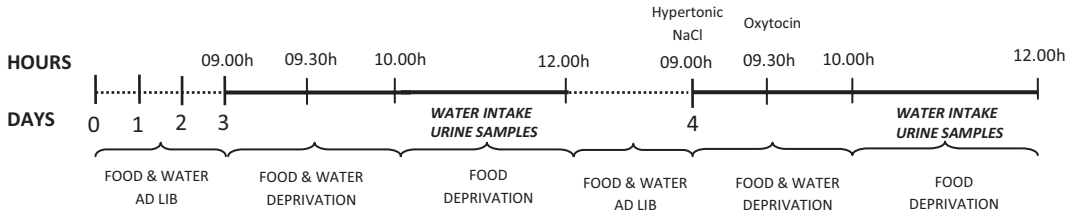

Fig. 1. Timeline of experiment 1 procedures.

3. Results

3.1. Experiment 1

3.1.1. Baseline

Results obtained during the baseline period show no differences between DW and OT groups in urine volume, urinary sodium or potassium concentration or excretion, or estimated plasma sodium concentration (Table 1).

3.1.2. Effects of OT on water intake induced by hypertonic NaCl administration

The results of this experiment demonstrate the effect of NaCl and OT administration on water intake ($F[1,12] = 67.59$; $p < 0.01$). *Post-hoc* analysis showed that NaCl administration increased the water intake (vs. baseline) of the control (NaCl/DW) animals ($p < 0.01$) but not of the OT-treated animals, and the water intake was significantly higher in the NaCl/DW than in the NaCl/OT animals ($p < 0.01$) (Fig. 3).

3.1.3. Effects of OT on urine volume, urinary sodium and potassium concentration and excretion, water and sodium balances, and estimated plasma sodium induced by hypertonic NaCl administration

NaCl administration increased the urine volume ($F[1,12] = 16.49$, $p = 0.01$) and produced a higher urinary sodium concentration ($F[1,12] = 21.65$; $p < 0.01$) and natriuretic response ($F[1,12] = 27.37$, $p < 0.01$) in OT-treated animals than in DW-treated animals (Table 1). However, no statistically significant difference in urinary potassium concentration or kaliuretic response was found between these groups (Table 1). Nevertheless, the water balance (Fig. 4; $F[1,12] = 156.47$; $p < 0.01$), sodium balance (Fig. 4; $F[1,12] = 25.96$; $p < 0.01$), and estimated plasma sodium concentration (Table 1; $F[1,12] = 8.38$; $p < 0.01$) were significantly lower in OT-treated than in DW-treated animals.

3.2. Experiment 2

3.2.1. Baseline

All animals showed a similar water intake during the baseline period (days 1–9, before any substances were administered), with a reduced intake during the days on a low-sodium diet (days 7–9) ($F[4156] = 3.46$; $p < 0.01$). Measurements taken between 18.00 and 20.00 h on days 7–9 showed that almost no water was consumed by any group: 0.04 ± 0.01 ml by the PEG/OT group, 0.14 ± 0.04 ml by the PEG/DW group; 0.14 ± 0.03 ml by the OT group, 0.00 ± 0.00 ml by the DW group, and 0.11 ± 0.03 ml by the ketamine group. Likewise, no differences were observed in the natriuretic (0.06 ± 0.01 mEq for both PEG/OT and PEG/DW animals) or kaliuretic (0.41 ± 0.03 mEq for PEG/OT and 0.39 ± 0.02 mEq for PEG/DW animals) response of the PEG-administered groups on days 7–9 (pre-treatment, low-sodium diet).

3.2.2. OT-related hydro-mineral regulatory responses after PEG administration

On the treatment day (day 10), the water intake between 18.00 and 20.00 h was significantly influenced by the administration of PEG and OT ($F[12,127] = 10.12$; $p < 0.01$). *Post hoc* analyses revealed a dipsogenic effect in PEG/DW and PEG/OT groups, with a water intake that was significantly higher ($p < 0.01$) during this period than during the pre-treatment days on low-sodium diet (days 7–9) and significantly higher than the water intake of the groups treated with OT, ketamine, or DW alone on day 10 ($p < 0.01$ for all comparisons) (Fig. 5). OT administration enhanced the dipsogenic effect of PEG, and the water intake measurements at 30 and 120 min were significantly higher ($p < 0.01$) in the PEG/OT group than in the PEG/DW group (Fig. 5).

Urine volume and water balance were significantly influenced by PEG administration on day 10 ($F[4,39] = 10.72$; $p < 0.01$ for urine volume and $F[4,39] = 9.74$; $p < 0.01$ for water balance). *Post hoc* analyses confirmed its antidiuretic effect, with significant differences in urine excretion between the treatment day and the previous two days ($p < 0.01$ day 10 vs. day 9 and day 10 vs. day 8). Although the urine volume excreted by the PEG/OT group was 4-fold lower, the difference with the PEG/DW group (Fig. 6B; 0.14 ± 0.04 ml vs. 0.60 ± 0.03 ml; $p < 0.1$) did not reach statistical significance. However, the water balance of the PEG/DW group was significantly higher than that of the groups not treated with PEG ($p < 0.01$) but lower than that of the PEG/OT group (Fig. 6C; $p < 0.05$). The marked antidiuretic effect observed on day 10 made it technically impossible to measure urinary sodium and potassium concentrations.

Furthermore, from 20.00 h on day 10 to 09.00 h on day 11, the water intake (Fig. 6D; $F(1,21) = 4.62$; $p < 0.05$) and urine volume (Fig. 6E; $F(1,21) = 6.31$; $p < 0.05$) were lower in the PEG-OT group than in the PEG-DW group. However, no significant differences were found between these groups in water balance (Fig. 6 F), urinary sodium concentration

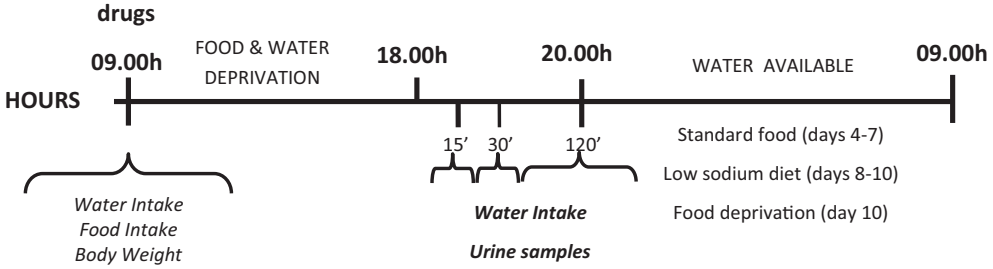

Fig. 2. Timeline of experiment 2 procedures.

Table 1
Urine volume (ml), urinary sodium and potassium concentration (mEq/l) and excretion (mEq) and estimated plasma sodium concentration (mEq/l) before (baseline) and after distilled water (DW) or oxytocin (OT) administration in rats pre-treated with hypertonic NaCl.

Group	n	Urine volume		Urinary sodium concentration		Urinary potassium concentration		Natriuresis		Kaliuresis		Plasma sodium estimated	
		Baseline	Experimental	Baseline	Experimental	Baseline	Experimental	Baseline	Experimental	Baseline	Experimental	Baseline	Experimental
Distilled water	7	1.64 ± 0.3	3.36 ± 0.2*	70.1 ± 9.9	374.36 ± 24.4*	166.76 ± 33.8	367.21 ± 20.6	0.10 ± 0.03	1.23 ± 0.06*	0.30 ± 0.09	1.21 ± 0.05	149.24 ± 4.6	149.57 ± 0.20*
Oxytocin	7	1.83 ± 0.5	5.21 ± 0.4	130.1 ± 42.3	622.43 ± 47.4	175.69 ± 26.3	304.47 ± 45.4	0.35 ± 0.16	3.25 ± 0.38	0.34 ± 0.11	1.64 ± 0.33	149.62 ± 0.4	145.98 ± 1.22

* $p < 0.01$ DW vs. OT.

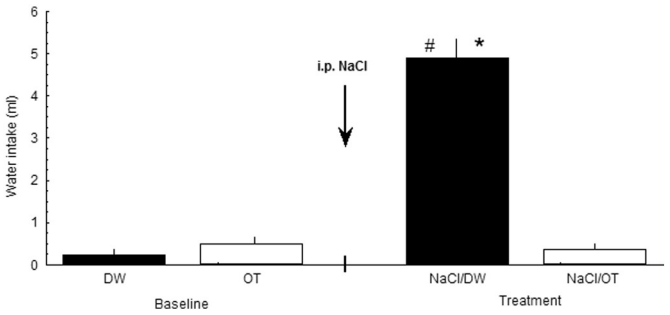

Fig. 3. Water intake for 120 min before (baseline) and after distilled water (DW) or oxytocin (OT) administration in rats pre-treated with hypertonic NaCl (#$p < 0.01$ baseline vs. treatment period; *$p < 0.01$ NaCl/DW vs. NaCl/OT).

(2.74 ± 1.17 mEq/l for PEG/OT and 1.77 ± 0.15 mEq/l for PEG/DW), natriuresis/sodium balance (0.008 ± 0.003 mEq for PEG/OT and 0.012 ± 0.001 mEq for PEG/DW), or estimated plasma sodium concentration (144.7 ± 1.48 mEq/l for PEG/OT and 143.6 ± 1.04 mEq/l for PEG/DW).

Finally, considering both time intervals together (i.e., from 18.00 h on day 10 to 09.00 h on day 11), no statistically significant difference in water intake (Fig. 6G) or water balance (Fig. 6I) was observed between the PEG/OT and PEG/DW groups. However, the volume of urine excretion was significantly lower in the PEG/OT group than in the PEG/DW group (Fig. 6H; $F[1,22] = 4.69$; $p < 0.05$).

4. Discussion

This study examined the hydro-mineral regulatory effects produced by OT under conditions of intra- and extra-cellular thirst. OT treatment was found to reduce the water intake induced by hypertonic NaCl administration and increase the water intake triggered by PEG administration.

NaCl administration increases the extracellular concentration of solutes, producing cellular dehydration at the same time as it triggers diverse behavioral and physiological regulatory responses, including water intake, antidiuresis, and natriuresis [2,18,24,39,52]. Thus, in the present experiment 1 and after administrating hypertonic NaCl, the control group animals excreted similar amounts of sodium to those previously injected. In the absence of food, this regulatory reaction generated a virtually neutral sodium balance (Fig. 4). However, with respect to NaCl/OT group, the water balance of NaCl/DW group (Fig. 4) increased both with higher water intake (Fig. 3) and with the antidiuretic effect induced by hypertonic NaCl (Table 1). It should be borne in mind that both sodium and water balances need to be narrowly coordinated to maintain plasma sodium levels.

These results contrast with the data obtained in the OT-treated animals that had also previously received a hypertonic NaCl solution. Indeed, in comparison to the NaCl/DW group, the OT treatment increased the concentration and excretion of urinary sodium (Table 1) in response to hypertonic NaCl, producing a negative sodium balance (Fig. 4). This

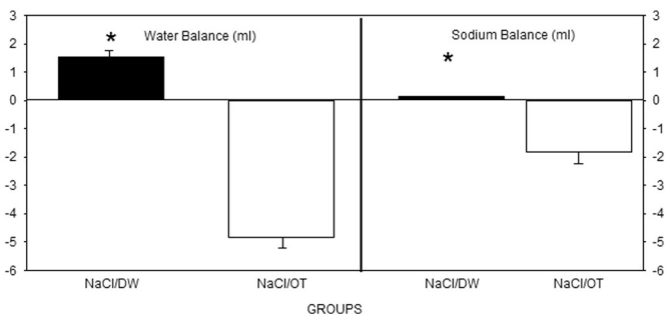

Fig. 4. Water and sodium balances after distilled water (DW) or oxytocin (OT) administration in rats pre-treated with hypertonic NaCl. (*$p < 0.01$ NaCl/DW vs. NaCl/OT).

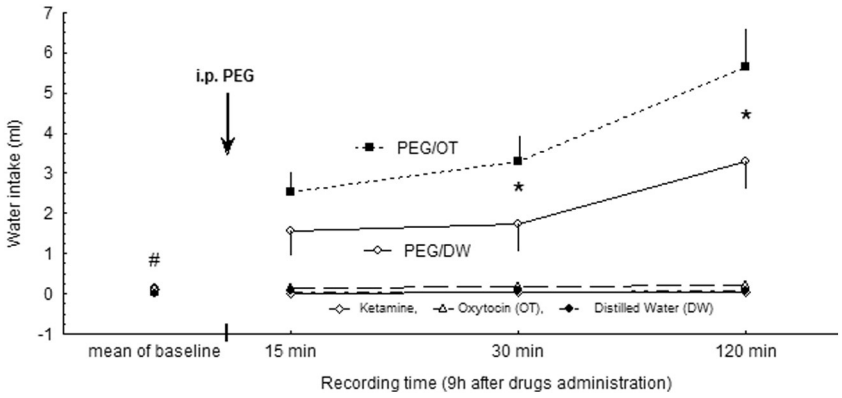

Fig. 5. Water intake for 120 min before (baseline) and 9 h after DW or OT administration in animals pre-treated at 09.00 h with polyethylene glycol (PEG) and after treatment with OT, DW, or ketamine alone (#p < 0.01 baseline vs. treatment period for PEG-treated groups; *p < 0.01 PEG/DW vs. PEG/OT).

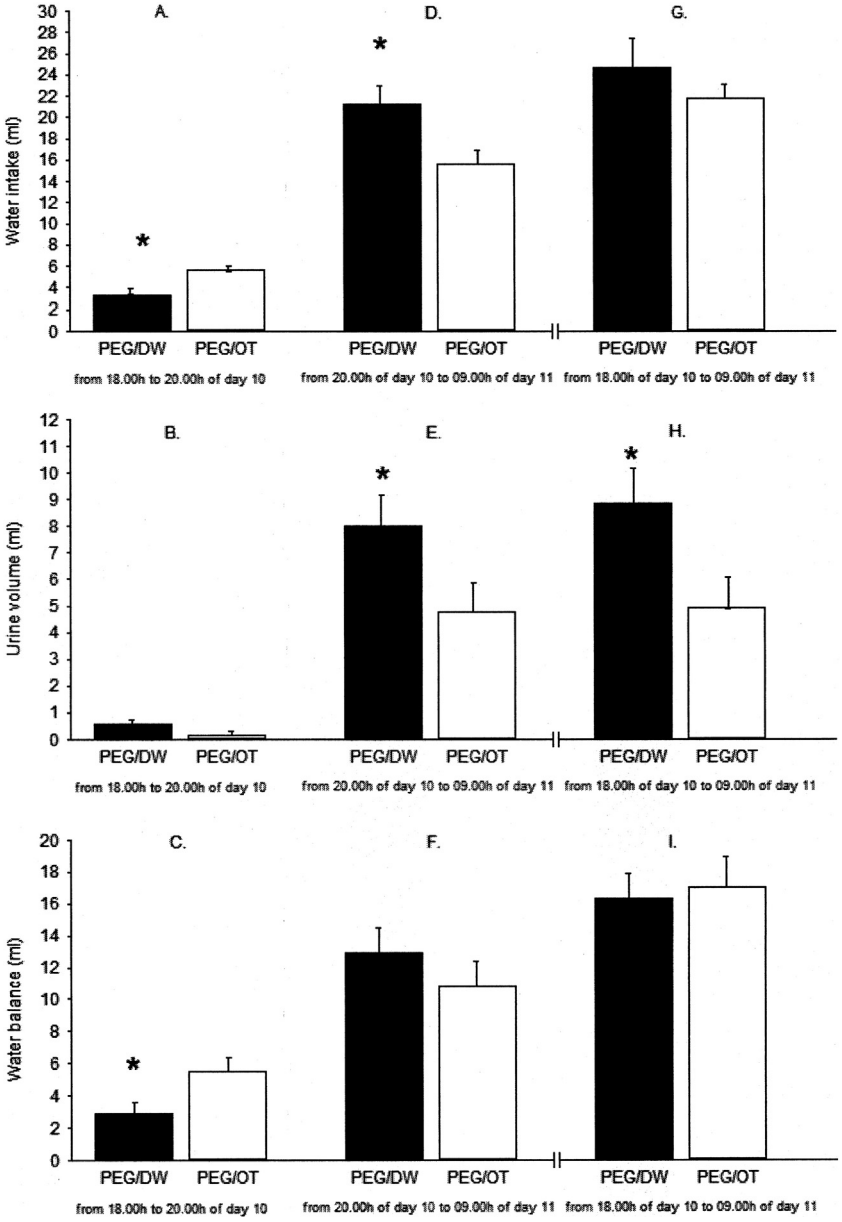

Fig. 6. Water intake (A, D, G), urine volume (B, E, H), and water balance (C, F, I) after distilled water (DW) or oxytocin (OT) administration in rats pre-treated with polyethylene glycol (PEG) (*p < 0.05 PEG/DW vs. PEG/OT).

natriuretic effect under situations of intracellular dehydration appears to be characteristic of the neurohormone through action on kidney OT receptors [36,37]. Likewise, there was an increase in the urine volume excreted by the OT-treated animals (Table 1; [20,85]), which, in the absence of a compensatory water intake (Fig. 3), also resulted in a decreased water balance (Fig. 4). Specifically, these negative water and sodium balances reduced the estimated plasma sodium levels in the NaCl/OT group versus the NaCl/DW group (Table 1). This suggests that OT may induce a reduction in body sodium that blunts the water intake that would normally be induced by hypertonic NaCl [80,81], which in turn may indirectly prevent correction of the resulting water imbalance.

Previous studies on the relationship among OT, water intake, and sodium intake/excretion found that OT stimulates the water intake of rats that are food-deprived or on low sodium diets but not of those on a standard sodium-containing diet available ad lib [10]. In addition, the water intake induced in a dose-dependent manner by OT administration was always preceded by an increase in the secretion of sodium [8,10,11] and reduced in a dose-dependent manner by the administration of hypertonic NaCl [8]. These findings suggest that NaCl administration (or dietary intake) prevents development of the dipsogenic effect of OT and, conversely, the dipsogenic effect of OT administration is reduced by NaCl. Taken together, all of these studies highlight the possible importance of sodium availability in the analysis of these regulatory processes, consistent with the fact that sodium and its attendant ions account for an estimated 90–95% of the osmotically active particles in plasma. This supports the proposal that water intake is fundamentally a sodium-related behavior [17,39,84].

Results obtained in experiment 2 show the dipsogenic effect induced by PEG in the control group (Fig. 5; [7,66]) and demonstrate that this effect may be enhanced after the additional administration of OT (Fig. 6A). The water intake generated by PEG administration appears to be hypovolemic and involves a delayed induction of NaCl consumption [73,74]. Thus, the intake of water and NaCl is increased by the combined treatment with PEG and OT [77]. In this regard, the action of OT has been also related to renin secretion [38] and hypotensive effects [31,32]. Therefore, the dipsogenic effect of OT in PEG-treated rats may be related to the renin–angiotensin–aldosterone system [25,28,29,79] and/or cardiovascular mechanisms [4,27,67,71,78], although the specific physiological mechanisms involved have not yet been elucidated.

The present study also shows an intense antidiuretic effect of PEG between 18.00 and 20.00 h on treatment day [7,23,64,65], which prevented the effect of OT from reaching statistical significance (Fig. 6B), despite the 4-fold reduction in urine excretion volume. However, the combination of increased water intake and decreased urine volume induced by OT in PEG-treated rats gave rise to a significant increase in the water balance (Fig. 6C).

Subsequently (from 20.00 h on treatment day to 09.00 h on the next day), the water intake of PEG/OT-treated animals was significantly inhibited in comparison to PEG/DW animals (Fig. 6D). Compensatory responses for the effects of OT on water intake were previously observed [8,11] and have also been reported for intraoral glucose intake [47], food intake and body weight [13], and other regulatory processes (e.g., arterial pressure) [54].

The intake inhibition shown by PEG/OT animals, which could be a result of the previous osmotic dilution [72], is accompanied by a significant increased urine retention (vs. PEG/DW animals; Fig. 6E) [76]. The antidiuretic effect of OT along with a reduced water intake allows the PEG/OT group to recover and maintain a similar water balance to that of the PEG/DW group (Fig. 6F). These antidiuretic effects of OT have been related to vasopressin V2 receptors but not to OT receptors [19,20,34,46,58,63], suggesting that hypovolemia may have evoked a state-dependent switch in kidney function, favoring actions mediated by the V2 but not OT receptor (in agreement with [70]).

The two groups of PEG-treated animals showed (from 20.00 h on day 10 to 09.00 h on day 11) a natriuretic response close to zero [7,76], possibly favored by the previous consumption of a low sodium diet. Hence, by excreting similar amounts of urinary sodium and having recovered their water balance (reduced water intake plus increased antidiuresis), the estimated plasma sodium of the PEG/OT-treated animals is similar to that of the control group (PEG/DW).

The successive sequence of regulatory adjustments produced by OT in PEG-treated animals (from 18.00 h on treatment day to 09.00 h on the following day), which finally results in a similar water intake (Fig. 6G) and water balance (Fig. 6I) to those of the PEG/DW group, means that the PEG/OT animals must resort to a greater antidiuretic response (Fig. 6H).

Unlike the present experiment, other studies in which PEG-treated animals had both hypertonic NaCl and water available show that the dipsogenic effect of OT is accompanied by augmented renal sodium losses [77]. Therefore, sodium availability and body levels appear to determine the physiological actions underlying the regulatory effect of OT on water intake. Thus, the increased natriuretic response observed in experiment 1 and in PEG/OT treated rats with NaCl availability [77] contrasts with the antidiuretic effect induced in PEG/OT-treated rats with no NaCl availability (experiment 2). Hence, the affinity of OT for OT or vasopressin receptors [53] may have a differential regulatory function in states associated with higher or lower body sodium levels.

The natriuretic and antidiuretic effects of OT associated with water intake behavior have been observed in different situations. Studies of neurological disorders that hinder body sodium excretion showed that OT augmented natriuresis in hypophysectomized [6] and neurohypophysectomized animals [5] and increased sodium excretion and reduced polydipsic behavior in animals with electrolytic lesions of the medial tuberomammillary nuclei [49] and mediobasal hypothalamus [9,48]. The natriuretic effect of OT in humans is controversial [43,59], and most studies have centered on the antidiuretic effect of OT (see [63]). In fact, recognition of the antidiuretic effect of OT is based on clinical observations in obstetric patients receiving systemic infusion of high-dosage OT, resulting in water intoxication [56,57,83]. OT exerts antidiuretic activity and contributes to hyponatremia in certain clinical settings, in which V2 receptor antagonists may be useful in the differential diagnosis and treatment of inappropriate antidiuresis [1,63]. Finally, the regulatory response of polydipsic patients [35] and animals [21] was improved by administration of Pituitrin, an extract of the bovine posterior pituitary that contains OT and vasopressin.

In summary, the results of this study indicate that OT may reduce water intake and increase natriuresis in states of body sodium excess (intracellular dehydration thirst) and may increase water intake and reduce urine volume in situations of body sodium loss (volemic thirst). Given that central OT was found to inhibit water intake and sodium appetite [3,14–16,22,60] and the difficulty of this neurohormone to reach the brain [41], it appears likely that the hydromineral regulatory action that may be developed by OT takes place at peripheral level via mechanisms that are yet to be determined.

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