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Short-term cross-sensitizion of need-free sugar intake by combining sodium depletion and hypertonic NaCl intake

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ABSTRACT

History of sodium depletion cross-sensitizes the effects of drugs of abuse. The objective of the present study was to find out if history of sodium depletion also cross-sensitizes a natural reward such as sugar intake in the rat. Sodium depletion was induced by furosemide combined with removal of ambient sodium for 24 h; it was repeated seven days later. The depletion was immediately followed by 0.3 M NaCl intake in a sodium appetite test (active sodium repletion). Seven days after the last depletion, hydrated and fed (need-free) sucrose-naïve animals were offered 10% sucrose in a first 2-h sucrose test. The sucrose test was repeated once a day in a series of five consecutive days. History of sodium depletion enhanced sucrose intake in the first and second tests; it had no effect from the third to fifth sucrose test. The effect on the initial sucrose intake tests disappeared if the rats did not ingest 0.3 M NaCl in the sodium appetite test. Prior experience with sucrose intake in need-free conditions had no effect on sodium appetite. History of intracellular dehydration transiently influenced sucrose intake in the first sucrose test. We found no evidence for thirst sensitization. We conclude that history of dehydration, particularly that resulting from sodium depletion, combined to active sodium repletion, produced short-term cross-sensitization of sucrose intake in sucrose-naïve rats. The results suggest that the cross-sensitization of sucrose intake related with acquisition of sugar as a novel nutrient rather than production of lasting effects on sugar rewarding properties.

1. Introduction

Sodium appetite guides a sodium-depleted animal to ingest selectively the lost nutrient (Epstein, 1991). Such example of ingestive behavior directed to a specific goal is fundamental to restore the volume of the extracellular compartment. Sodium depletion in humans occurs in response to episodic dehydration, such as that found, for example, during exercise (Hew-Butler, Verbalis, & Noakes, 2006). In the rat, sodium depletion releases natriorexigenic hormones (angiotensin II, aldosterone) which not only induce sodium appetite, but also reorganize the brain and future behavior (Bernstein, 2003; Epstein, 1991; Hurley & Johnson, 2013; Pereira, Menani, & De Luca, 2010; Sakai, Fine, Epstein, & Frankmann, 1987). One consequence of such reorganization is selective enhancement of the ingestion of sodium solutions in response to future sodium depletions (Pereira et al., 2010; Sakai et al., 1987). It corresponds to sensitization, a kind of non-associative learning which is produced by stimulus repetition (Bernstein, 2003; Dietz, Curtis, & Contreras, 2006; Olsen, 2011). The capacity to enhance sodium intake presumably reflects an evolutionary adaptation to environmental sodium lack, thus reducing the risks associated with extracellular dehydration (Epstein, 1991).

Similar to sodium, sugar or sweeteners added to water provides a strong reward for an animal with internal deficits such as the dehydrated rat (Cabanac, 1992; De Luca, Pereira-Derderian, Vendramini, David, & Menani, 2010; Epstein, 1991). Rats in need-free conditions, fed and hydrated, and with no recorded history of nutritional deficits, also ingest substantial amounts of sugar (De Luca, De Souza, Yada, & Meyer, 1999; Smith & Sclafani, 2002). Need-free sugar intake avoids the confounding effects that lack of nutrients might have on the expression of the behavior. In other words, we have a behavior guided mainly by the rewarding properties of the goal. Rewarding or hedonic properties in conditions of plenty have a link to pathological consumption of nutrients, particularly sodium and sugar (DiNicolantonio & Lucan, 2014; Hu &

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Malik, 2010; Tekol, 2006).

Common reward circuits overlap in the brain potentially subserving interactions among motivated behaviors (Bernstein, 2003; Berridge, 2009; Grigson, 2002; Olsen, 2011). Cross-sensitization is one of those interactions, and sodium appetite as well as the motivation to ingest sugar cross-sensitize the effects of drugs of abuse. For example, prior experience of sodium depletion enhances the ambulatory effects of amphetamine, cocaine or morphine in rats (Acerbo & Johnson, 2011; Clark & Bernstein, 2004; Na, Morris, & Johnson, 2009). Prior experience with these drugs also sensitizes sodium appetite. Equivalent reciprocal cross-sensitization occurs between sucrose intake and drugs of abuse (Avena, Rada, & Hoebel, 2008). Thus, it is of interest to know whether the conditions that produce sodium and sugar intake also interact.

Considering that sodium depletion cross-sensitizes the effects of artificial rewards such as drugs of abuse, we asked whether history of sodium depletion also sensitizes the need-free intake of a natural reward such as sugar. We investigated whether enhanced sucrose intake follows the enhancement of sodium appetite in the rat. We also investigated whether the enhanced sucrose intake is persistent, and reciprocal sensitization occurs between sucrose intake and the production of sodium appetite. Finally, we investigated whether the ingestion of hypertonic NaCl in sodium appetite tests is necessary for the enhancement of sucrose intake, and whether intracellular dehydration sensitizes water and sucrose intake.

2. Methods

2.1. Animals

Male Holtzman rats from the Araraquara colony at UNESP, weighing between 270 and 280 g upon arrival, were used. They were maintained on a 12:12 light/dark cycle, individually housed in wire mesh suspended cages in temperature and humidity controlled rooms, and gently handled daily. Two polypropylene bottles (100 ml capacity with divisions to the nearest ml) with stainless steel spouts, each containing water and 0.3 M NaCl, were freely available per cage unless otherwise noted. Rodent food chow pellets (1% sodium; BioBase, Brazil) were available for the rats in a container hanging outside of each cage. The tests of all experiments began between 9 and 12 a. . m., 7 days after housing the animals with all fluids available. The protocols were approved by the Institutional Animal Care and Use Committee (CEUA FOAr, UNESP) and followed the recommendations from the National Council for the Control of Animal Experimentation (CONCEA).

2.2. Solutions

Sucrose and NaCl were dissolved in filtered tap water.

2.3. Drugs

Furosemide (diuretic and natriuretic, Sigma-Aldrich St. Louis, MO) was dissolved (10 mg/ml) in distilled water (vehicle) at a pH adjusted to 9.0 with 0.1 M NaOH.

2.4. Sodium depletion and sodium appetite test

Food, 0.3 M NaCl and water was removed and the rat's cage rinsed with water. Next, sodium depletion was induced by one subcutaneous injection of furosemide (10 mg/ml/rat) followed by access to only water and sodium-deficient food (powdered corn meal; 0.001% sodium and 0.33% potassium) for 24 h. This procedure induces between 1.5 and 2.0 mEq loss of sodium and consistent sodium appetite, which expresses or "matures" several hours after the injection of furosemide (Rowland & Morian, 1999). A control group received subcutaneous injection of vehicle and had access to water, 0.3 M NaCl and regular food chow for 24 h.

Twenty-four hours after the furosemide or vehicle injection, the food was removed and 0.3 M NaCl and water were offered to the animals in 0.1 ml graduate glass burettes fitted with stainless steel spouts. The animals were warned of the presence of fluids by gentle prodding of their lips with the spout. The intake of each fluid was measured at 15, 30, 60 and 120 min (sodium appetite test). The sodium appetite test is enough to restore blood volume and the sodium lost (Sakai et al., 1987). Standard food was returned to all animals after the test and remained available with water and 0.3 M NaCl until the next sodium depletion.

2.5. Sucrose test

As detailed in Experiments 1, 2 and 4, sucrose solution was offered daily to hydrated and fed animals beginning one week after the last sodium appetite test (Experiments 1 and 2) or thirst test (Experiment 4). The animals were naïve to sucrose solution when they entered the first sucrose intake test and the sucrose test was repeated once a day in a series of five tests.

In a slight modification of a sugar test described previously (De Luca Jr. et al., 1999), water, 0.3 M NaCl and food were removed. Immediately thereafter, 10% sucrose was offered to the animals in 0.1 ml graduate glass burettes fitted with stainless steel spouts. The animals were warned of the presence of sucrose by gentle prodding of their lips with the spout of the drinking tube. Sucrose intake in hydrated and fed (need-free) conditions was recorded for 2 h (sucrose intake test). The 10% sucrose was removed at the end of the sucrose test, and food, water and 0.3 M NaCl were returned and remained available until the next test.

2.6. Statistics

Two-way repeated measures ANOVA was used for comparison of the means followed by the Student-Newman-Keuls post-hoc test. A probability of less than 0.05 was required for significance. Data are expressed as means $\pm$ standard error of the mean.

2.7. Experiment 1. Sucrose test in animals with history of sodium depletion and sodium appetite tests

The objective of this experiment was to test if history of sodium depletion sensitizes sugar intake.

Animals were separated into two groups, those to have no history of sodium depletion (control, $n = 8$), and those to have history of sodium depletion and actively replacing their sodium loss by ingesting 0.3 M NaCl in the sodium appetite test (His/AR, $n = 8$). The His/AR group was submitted to a first sodium depletion and sodium appetite test as described above. Standard food was returned after the sodium appetite test to all animals and remained available continuously with water and 0.3 M NaCl until the next depletion induced one week later. A second sodium appetite test was performed after the second sodium depletion. One week after the second sodium depletion, standard food, 0.3 M NaCl and water were removed, and a bottle containing 10% sucrose was attached to the front of the cage thus starting the sucrose test series.

2.8. Experiment 2. Sucrose test in animals with history of sodium depletion, but no sodium appetite test

As shown in Results, history of sodium depletion enhanced 10% sucrose intake in Experiment 1. The objective of Experiment 2 was to test if the experience with the ingestion of sodium in the sodium