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Olfactory bulbectomy impairs the feeding response to 2-deoxy-D-glucose in rats

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Abstract

An early study reported that, unlike sham-operated rats, rats made anosmic by olfactory bulbectomy (OBX) failed to compensate for the dilution of their diet with nonnutritive bulk by increasing their food intake. In the present study, the effects of a glucoprivic challenge, intraperitoneal-administered 350 mg/kg 2-deoxy-D-glucose (2-DG), on food intake were measured in OBX and sham-operated female rats. Sham-operated rats significantly increased their food intake, but in two separate experiments OBX rats displayed no increase in food intake during the first 2 h following administration. Blood glucose levels were nearly identical in both groups. Body weights and daily food intakes of OBX rats did not differ from the sham-operated controls throughout the studies. Bulbectomized rats also displayed a normal drinking response after an intraperitoneal injection of 1 M hypertonic saline. Hypothalamic nuclei and the neural pathways mediating taste have been implicated in the feeding response to 2-DG. The present results suggest that olfactory input and olfactory neural pathways also mediate, at least in part, the feeding response to a glucoprivic challenge induced by intraperitoneal injection of 2-DG.

Keywords

Olfactory bulbs; Glucoprivic challenges; Anosmia; Food intake; Water intake

1. Introduction

In order to survive, it is necessary that organisms respond to glucoprivation. Normal animals respond to administration of 2-deoxy-D-glucose (2-DG), a competitive inhibitor of intracellular glucose utilization, with a rapid increase in food intake. The etiology of the

feeding response to 2-DG has been studied extensively. It has been demonstrated that hindbrain catecholamine projections to the arcuate nuclei and the paraventricular nuclei of the hypothalamus are critical for the feeding response to 2-DG (Fraleay and Ritter, 2003; Hudson and Ritter, 2004; Li and Ritter, 2004; Li et al., 2006; Ritter et al., 1998, 2001). However, lesions of many other areas of the brain also impair the feeding response to 2-DG. These include the parabrachial nucleus (Tordoff et al., 1982), ventrobasal thalamus (Neill and Kaufman, 1977), central amygdaloid nucleus (Ritter and Hutton, 1995; Tordoff et al., 1982), and lateral hypothalamus (Balagura and Kanner, 1971; Epstein and Teitelbaum, 1967; Grossman and Grossman, 1982; Müller et al., 1974; Wayner et al., 1971). All of the latter nuclei are part of the visceral-taste pathway (see Tordoff et al., 1982, for a review).

Olfaction is a major component of the chemosensory systems, and elimination of olfactory cues affects feeding behavior. Removal of the olfactory bulbs (OBX) alters the typical rodent feeding pattern of distinct meals followed by long intermeal intervals to that of frequent small meals (Meguid et al., 1993) or a persistent nibbling pattern (Larue, 1975a; Larue and Le Magnen, 1971, 1972) in the first several weeks following surgery. Rats with OBX also do not respond normally to changes in their diet. They lose their ability to discriminate among different foods (Le Magnen, 1969), including their preference for highly palatable foods (Larue and Le Magnen, 1967; Primeaux et al., 2003).

The changes in feeding pattern after OBX normally do not result in decreases in total daily food intake or body weight in female rats (e.g., Larue and Le Magnen, 1970, 1972; Stock et al., 2000; Vance, 1967), and overconsumption and/or excessive weight gains have even been reported under certain conditions (Larue and Le Magnen, 1970; Zukerman et al., 2009). On the other hand, Larue and Le Magnen (1967) found that rats with OBX (unlike control animals) did not increase their food intake during several days when their powder diet was diluted with 25% nonnutritive cellulose. This suggests that rats with OBX may not respond normally to caloric challenges.

The present study attempted to extend our understanding of the role of olfaction and the olfactory bulbs on the response to a glucoprivic challenge (2-deoxy-D-glucose) using rats that were made anosmic by OBX.

2. Results

2.1. Experiment 1: effects of OBX on the feeding response to 2-DG

OBX did not abnormally affect body weight compared to SHAM controls either in the immediate postoperative period or long term. The OBX rats weighed 276.8 ± 3.1 g preoperatively and 286.6 ± 4.4 g on Day 35, compared to 271.9 ± 2.7 g and 282.5 ± 3.6 g, respectively, for the SHAM control animals.

The feeding responses after injections of 2-DG and saline are shown in Fig. 1. ANOVA revealed a significant effect for Condition ($F=7.87$, $df=1, 18$, $p<0.05$) and the Groups $\times$ Hour Interaction ($F=4.93$, $df=1, 18$, $p<0.05$). Individual comparisons revealed that the SHAM animals displayed a significant 2-DG-induced increase in feeding (compared to after saline injections) in the first hour after injection ($p<0.05$). Administration of 2-DG,

compared to saline, did not increase food intake in the OBX rats. None of the OBX rats consumed over 1.5 g in the first hour after 2-DG injections (compared to seven SHAM control animals).

The feeding responses in the second hour after injections were more variable and none of the differences were statistically significant. Five SHAM and three OBX rats consumed 1.5 g or more after 2-DG injections. Others ate very little or no food during the second hour.

2.2. Experiment 2: Comparison of effects of OBX on the feeding response to 2-DG and the drinking response to hypertonic saline

There were no statistically significant differences in the feeding or drinking responses after the two isotonic saline injections, and thus the mean responses were used as the baselines. The feeding responses to 2-DG are shown in Fig. 2. ANOVA for the feeding response to 2-DG revealed a significant effect for Condition ($F = 8.645$, $df = 1$, 17 , $p < 0.01$), Hour ($F = 12.340$, $df = 1$, 17 , $p < 0.01$), and Groups $\times$ Hour Interaction ($F = 6.641$, $df = 1$, 17 , $p < 0.05$). The SHAM animals nearly doubled their food intake in the first hour after 2-DG (0.9 ± 0.2 g vs. 1.7 ± 0.2 g). Neither group showed a significant increase during the second hour (0.5 ± 0.1 g vs. 0.7 ± 0.2 g for SHAM and 0.5 ± 0.1 g vs. 0.7 ± 0.2 g for OBX animals). As in Experiment 1, there were no significant differences in body weight throughout the experiment.

ANOVA for the drinking response to 1 M NaCl revealed significant effects only for Condition ($F = 36.16$, $df = 1$, 17 , $p < 0.001$) and Hour ($F = 38.70$, $df = 1$, 17 , $p < 0.001$), thus indicating there were no significant differences between the two surgical groups (Fig. 3). Two SHAM rats drank more than any of the other animals, but the other seven SHAM rats drank similar amounts of water as the OBX rats. Only two animals in each group ate any food during the first 2 h after injection of hypertonic saline.

2.3. Experiment 3: effects of 2-DG on blood glucose levels

Blood glucose levels following an injection of 2-DG (i.p.) are shown in Fig. 4. A mixed ANOVA revealed a significant effect for Time ($F = 172.68$, $df = 8$, 168 , $p < 0.001$), but not for Groups ($F = 0.282$, $df = 1$, 21 , $p = 0.601$). Blood glucose levels for the two groups were nearly identical at each 15-min interval.

3. Discussion

The purpose of the present studies was to investigate the role of the olfactory bulbs in the response to a glucoprivic challenge. Removal of the olfactory bulbs attenuated the normal feeding response to an injection of 350 mg/kg 2-DG when 2-DG was administered 32 days following OBX (see Fig. 1) and when administered 22 days following OBX (see Fig. 2). There was no damage to the frontal lobes.

The failure of rats with OBX to respond to 2-DG was not due to a difference in blood glucose levels. Intraperitoneal injection of 350 mg/kg 2-DG resulted in hyperglycemia in both OBX and SHAM animals. Blood glucose levels were nearly identical throughout the first 2 h after injection. The results from the current studies also cannot be attributed to a general debilitating effect of OBX on feeding behavior because body weight and daily food

intake of the rats with OBX were similar to SHAM rats throughout the study. Rats injected with insulin or 2-DG are hyperreactive to aversive diets (e.g., see Vasselli and Sclafani, 1979), but the normal daily food intake of OBX rats in the present study suggests that the animals did not find their standard rat chow diet to be aversive.

The normal drinking response by OBX rats following an i.p. injection of 1 M hypertonic saline demonstrates that they were also not deficient in all homeostatic responses (see also Wilcove and Vance, 1972). A preliminary study from this lab indicated that the feeding response of OBX rats to i.p. injection of insulin is also not as impaired as observed after injection of 2-DG.

Female rats were used in the present study because the results of previous studies indicated that OBX had little or no effect on body weight or weight gain in female rats (e.g., Larue and Le Magnen, 1970, 1972; Stock et al., 2000; Vance, 1967), as opposed to weight loss in males (e.g., Kelly et al., 1996; Primeaux et al., 2007). Two studies found that OBX had either no effect on estrous cycling in female rats (Stock et al., 2000) or only a very transient effect, lasting a maximum of four to five cycles (Larsson, 1977). Thus, the injections of 2-DG given in the present study (on Days 22 and 32) were administered well after the time when normal cycling was reported to have resumed.

Although the results of this initial study suggest that olfactory bulbectomy impairs the response to 2-DG, some questions must be addressed in future studies. For example, it is possible that different results would have been obtained with different dosages of 2-DG. However, the dosage selected for this initial study was that which previous experience had shown would result in a maximal feeding response in normal animals (King and Grossman, 1977). It would also be important to see if rats with OBX have a delayed response to 2-DG, as is found for rats with some medial hypothalamic lesions (King et al., 1978; Ritter et al., 1981).

The foremost question, of course, is why olfactory bulbectomy impairs the feeding response to 2-DG. One possibility is that the results were due to anosmia. Olfactory bulbectomy does not guarantee that rats become anosmic (Slotnick and Bodyak, 2002). However, two criteria, including a behavioral test, were used in the present study to determine the completeness of OBX, and rats had to fulfill both criteria to be included in the study. The OBX rats were unable to locate buried sweetened milk, although they had quickly consumed milk in their home cages. In previous studies, the changes in feeding pattern observed in the first few weeks after OBX (Larue, 1975a; Larue and Le Magnen, 1971, 1972; Meguid et al., 1993) were not found after transection of the vomeronasal nerve (Larue and Le Magnen, 1973), but were observed after zinc sulfate was applied to the olfactory mucosa (Larue, 1975b), suggesting that the changes were the result of ablation-induced anosmia and not to loss of other functions of the olfactory bulbs. A small pilot study conducted by King and colleagues suggests that rats made anosmic with zinc sulfate also do not respond to 2-DG. It should also be noted that the feeding response to 2-DG is abolished by lesions of nuclei throughout the visceral-taste pathway (see Tordoff et al., 1982, for a review). This includes the parabrachial nucleus (see Tordoff et al., 1982), ventrobasal thalamus (Neill and Kaufman, 1977), central amygdaloid nucleus (Ritter and Hutton, 1995; Tordoff et al., 1982), and lateral

hypothalamus (Balagura and Kanner, 1971; Epstein and Teitelbaum, 1967; Grossman and Grossman, 1982; Müller et al., 1974; Wayner et al., 1971). Taste is determined by olfactory cues as well as by sensory stimuli from the tongue (Faurion, 2006).

Another possibility is that OBX abolished the response to 2-DG because of its effect on noradrenergic responses. Olfactory bulbectomy is known to substantially decrease brain noradrenalin levels (e.g., Masini et al., 2004; Song and Leonard, 2005; van Riezen and Leonard, 1990), and noradrenergic pathways from the hindbrain to the arcuate and hypothalamic paraventricular nuclei have been shown to be essential for the feeding response to 2-DG (e.g., Fraley and Ritter, 2003; Hudson and Ritter, 2004; Li et al., 2006; Ritter et al., 1998, 2001). Olfactory bulbectomy increases preprogalanin mRNA levels in the locus coeruleus of rats (Holmes and Crawley, 1996) and increases preproneuropeptide Y levels in the hypothalamus (Primeaux et al., 2007). Lesions of the central and medial nuclei of the amygdala also abolish the feeding response to 2-DG and other glucoprivic challenges (King, 2006; King et al., 1998; Ritter and Hutton, 1995; Tordoff et al., 1982; see also King et al., 1993), and those nuclei receive projections from the olfactory bulbs and then project to hypothalamic nuclei (de Olmos, 1972; Lammers, 1972). Olfactory bulbectomy affects both serotonergic and preproneuropeptide Y activity in the amygdala (Primeaux et al., 2007; Rutkoski et al., 2002; van der Stelt et al., 2005). Olfactory bulbectomy affects a variety of other neurotransmitter and endocrine responses (see Song and Leonard, 2005, and Wang et al., 2007, for reviews). This includes ventral striatal dopamine systems (Masini et al., 2004) and limbic neuropeptide Y activity (Primeaux and Holmes, 2000).

In summary, two studies have now found that olfactory bulbectomized rats, unlike normal animals, did not increase their food intake after a caloric or glucoprivic challenge (Larue and Le Magnen, 1967; present study). The present results suggest that the ability of rats to respond to 2-DG is affected by olfactory bulb projections, but it remains for future research to determine the etiology of this deficit.

4. Experimental procedures

4.1. Animals

Seventy-three adult (90 days old) female Long-Evans hooded rats were used (Harlan, Indianapolis, IN). All animals were individually housed in standard wire-mesh rat cages (24 cm long×18 cm wide×18 cm high) in a temperature-controlled colony (21–24 °C) with a 12:12-h light–dark cycle (lights on at 7:00 a.m.) throughout the experiment. The study was approved by the University of New Orleans All University Committee for the Protection of Animal Subjects and the Pennington Biomedical Research Center Institutional Animal Care and Use Committee.

4.2. Olfactory bulbectomy

Olfactory bulbectomies were performed while the rats were anesthetized with 85 mg/kg ketamine HCl (plus 10 mg/kg xylazine). The scalp was shaved, and following a midline incision, two 2-mm diameter burr holes were drilled 1 mm to the right of the midsagittal suture beginning 6 mm anterior to bregma and a third 2-mm hole was drilled 1 mm to the left of the midsagittal suture (resulting in an L-shaped pattern). Bulbectomies were

performed by aspiration with a 2-mm diameter pipette tip and the cavity was filled with gelfoam (Upjohn, Kalamazoo, MI) to control bleeding. Special care was taken to avoid damaging the frontal cortex. Sham operated (SHAM) controls were treated similarly except that the olfactory bulbs were not removed.

Two criteria were used for anosmia. First, following sacrifice the remaining olfactory bulb tissue was weighed and an olfactory bulb tissue weight of less than 30% of the tissue weight of an intact olfactory bulb was required for possible inclusion in the study (Primeaux et al., 2007; Primeaux and Holmes, 1999). Additionally, all animals were given a behavioral test for anosmia, in which they were tested for their ability to locate an olfactory stimulus buried under bedding in a 102 cm×65 cm chamber. Prior to the test, they were habituated to the chamber for 30 min on 3 consecutive days and were allowed to drink up to 10 ml of Borden's condensed sweetened milk (2 parts water to 1 part milk) in their home cages on 2 consecutive days. For the test, the animals were food and water deprived for 24 h and were then given 10 min to locate buried sweetened milk (in a petri dish) (a series of pilot studies with stimuli commonly used in other OBX studies, e.g., cheese and male urine, showed this to be the most reliable behavioral test in terms of normal animals' ability to locate the stimulus). To be included in the study, the OBX rats had to satisfy both criteria.

4.3. Procedure

4.3.1. Experiment 1—Two groups were compared: an OBX group ($n=15$) and a SHAM group ($n=10$). The animals were fed a standard rodent diet (Harlan Teklad mouse/rat diet LM-485). All the animals were habituated to intraperitoneal (i.p.) injections for 3 days starting on postoperative Day 21. A 2-ml injection of isotonic saline was given on postoperative Day 24 and 350 mg/kg 2-DG was given on Day 32. Injections were given during the light cycle (2:00 p.m.), when rats normally consume only a small proportion of their 24-h intake. Food intakes were measured after the first and second hours following each injection by subtracting spillage (collected on paper towels under the cages) and any uneaten food remaining in the cages from the premeasured amounts supplied. Results were analyzed with a 3-way ANOVA (Groups × Condition × Hour) with repeated measures. Post hoc comparisons were done with Tukey's HSD test.

Two of the 15 rats given OBX died during the surgery. Of the remaining 13, three were found to have incomplete bulbectomies at the end of the study. Thus, statistical analyses were performed on 10 rats with OBX and 10 SHAM rats. None of the remaining OBX rats located the sweetened milk during olfactory stimulus behavioral testing (all had quickly consumed sweetened milk when it was given to them in their home cages). The mean weight of the remaining olfactory bulb tissue was only 13.3% of that of intact olfactory bulbs in SHAM rats.

4.3.2. Experiment 2—Two groups were compared: an OBX group ($n=15$) and a SHAM group ($n=10$). The animals were fed a standard rodent diet (Harlan Teklad mouse/rat diet LM-485). All animals were habituated to i.p. injections for 3 days starting on postoperative Day 8. An i.p. injection of 5 ml isotonic saline was given on Day 11 and an injection of 2 ml isotonic saline was given on Day 32. A 5-ml i.p. injection of 1 M NaCl was given on Day 17

and an injection of 350 mg/kg 2-DG was given on Day 22. Injections were given during the light cycle (2:00 p.m.) and feeding and drinking responses were measured after the first and second hours. Water intake was measured to the nearest ml. Results were analyzed with a 3-way ANOVA (Groups $\times$ Condition $\times$ Hour) with repeated measures.

Of the 15 rats given OBX, one died during surgery and four were found to have incomplete bulbectomies at the end of the study. All of the SHAM rats located the olfactory stimulus during behavioral testing, but none of the 10 OBX rats did so (all had quickly consumed sweetened milk when it was presented in their home cages). The mean weight of the remaining olfactory bulb tissue in OBX rats was only 11.2% of that of intact olfactory bulbs in SHAM animals. One of the SHAM control animals proved to be an outlier in terms of both initial body weight lost after surgery (26 g/4 days compared to a mean of 6.4 g $\pm$ standard deviation of 2.8 g for the other nine) and also by the fact that it did not respond at all to any of the feeding or drinking stimuli. Thus, statistical analyses were performed on 10 rats with OBX and 9 SHAM rats.

4.3.3. Experiment 3—Two groups were compared: an OBX group ($n=14$) and a SHAM group ($n=9$). The animals were habituated to the injection procedure using saline. Testing was conducted after an overnight fast 24 days after surgery. Blood was taken from the tail at 15-min intervals for 2 h after an i.p. injection of 350 mg/kg 2-DG. Glucose was measured using Glucometer Elite and Ascensia Elite blood glucose test strips from Bayer. All of the OBX rats were found to have complete bulbectomies.

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Fig. 1. Mean ($\pm$ SE) food intake of OBX rats and SHAM rats during the first (1 h) and second (2 h) hours after i.p. injections of saline or 350 mg/kg 2-DG. Asterisks indicate a significant increase in food intake ($p < 0.05$) compared to after the saline injection.

Fig. 2. Mean ($\pm$ SE) food intake of OBX rats and SHAM rats during the first (1 h) and second (2 h) hours after i.p. injections of saline or 350 mg/kg 2-DG. Asterisks indicate a significant increase in food intake ($p < 0.05$) compared to after the saline injection.

Fig. 3. Mean ($\pm$ SE) water intake of OBX rats and SHAM rats during the first (1 h) and second (2 h) hours after i.p. injections of isotonic saline or 1 M NaCl. Asterisks indicate a significant increase in water intake ($p < 0.05$) compared to after the injection of isotonic saline.

Fig. 4.
Mean ($\pm$ SE) blood glucose levels in OBX and SHAM rats during the first 2 h after an i.p. injection of 350 mg/kg 2-DG.