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Research report

The effects of FG 7142 on sensory-specific satiety in rats

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ABSTRACT

Three experiments used intake, clusters, and licks per cluster to study the effects of the GABA inverse agonist, FG 7142, on sensory-specific satiety in rats. In Experiment 1, rats were offered one of two palatable solutions and 30 min later tested with the same or the other solution. Rats that received the same solution consumed less, exhibited fewer clusters, fewer licks per cluster and a more rapid decline in rate of licking than rats tested with the other solution. In Experiments 2 and 3, rats tested with the same solution under FG 7142 showed fewer clusters and fewer licks per cluster than vehicle rats. Rats tested with the other solution under FG 7142 showed fewer licks per cluster but more clusters than vehicle rats. The results were discussed in terms of the distinction between "liking" and "wanting" and the role of GABA in the former but not the latter.

1. Introduction

Offered a choice between two equally palatable and familiar foods, one of which has been ingested to satiety, laboratory subjects select the other food for further ingestion. The sensory properties of the ingested food are said to have undergone satiety. Sensory-specific satiety is well documented. It has been observed in subjects from various animal species, including people, when they choose between any of a range of recently ingested foods and a relatively novel one, and when they choose between two foods identical in terms of their micronutrient (e.g., fat or protein) composition but differing in their flavor. Sensory-specific satiety is one of the mechanisms by which a diet containing different foods increases ingestion relative to one lacking that variety. Hence, it may be a contributor to the prevalence of obesity in a society where a range of high-calorie and high-fat foods are relatively cheap and readily available. Sensory-specific satiety may also be one of the mechanisms by which omnivores solved the problem of obtaining adequate nutrition from a range of different foods. This satiety could bias selection and ingestion of other foods in advance of complete metabolic satiety and, hence, allows extraction of nutrients from these other foods.

A food subjected to sensory-specific satiety does not just elicit less ingestion: such a food is also impaired in its ability to act as a reward for instrumental responses and as an unconditioned stimulus (US) for Pavlovian conditioned responses [6]. Indeed, the devaluation of a food by pre-feeding is a standard technique used to assess the role of response–reward or conditioned stimulus (CS)–US associations in the control of instrumental and Pavlovian responses [1,2]. Moreover, a recently ingested food also loses its ability to elicit oro-facial responses indicative of "liking". Taste reactivity measures in rats have shown that an oral infusion of a recently ingested flavor elicits less positive ingestive reactions (tongue protrusions, paw licking) than does infusion of a different flavor [3,13]. This decline in hedonics is transient, with its peak occurring in the period shortly after ingestion [10,16]. A recently ingested food elicits few, if any, aversive reactions (e.g., headshake, gaping) and does not produce an aversion to that food, indicating that ingestion produces a transient reduction in oro-facial responses indicative of liking. Such findings have led to the view that a recently ingested food suffers a transient loss in hedonics. This loss suppresses further ingestion of that food and promotes the selection of a different food whose palatability is largely intact.

GABA plays a critical role in the regulation of feeding behaviour [12,14]. Drugs, e.g., benzodiazepines, which facilitate activity at the GABA A receptor site, stimulate feeding in both deprived and non-deprived rats. This stimulation is likely due to the effects of these drugs on food hedonics as they increase both the preference for palatable solutions (e.g., sucrose) over water and the liking reactions elicited by an oral infusion of a palatable solution. Conversely, inverse agonists – which reduce activity at this site – depress ingestion of palatable food. For example, FG 7142 (*N*-methyl-β-carboline-3-carboxymide) reduces intake [8] and the duration of feeding bouts [4]. This effect of FG 7142 on ingestion is thus likely

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due to a reduction in food hedonics, but to the best of our knowledge, this remains unknown. Moreover, this effect of FG 7142 was observed in rats exposed to a single palatable food, but, again to the best of our knowledge, the effects of the drug have not been assessed in a sensory-satiety paradigm where the palatability of one but not another food has been reduced.

The present experiments studied the effects of FG 7142 on the hedonic responses to a palatable solution that has or has not been recently ingested. As noted, ingestive responses (e.g., tongue protrusions and paw licking) to an orally infused solution are one measure of positive hedonics. Another measure can be obtained from the distribution of licking responses to a solution. Licks are generated in bursts separated by pauses whose duration is used to form sequences and reveal the number of licking 'bouts' or clusters that occur across a meal [5]. The size and number of these lick clusters provide an index of hedonics [5,7]. For example, increased concentrations of sucrose produce corresponding increases in the number of bursts and hence in the size of the clusters [5] whereas bitter tasting solutions decrease cluster size [17]. We used this measure of hedonics. In three experiments, rats drank one of two palatable, familiar solutions and were then offered the same or the other solution. The aim of Experiment 1 was to demonstrate sensory-specific satiety. More specifically, the aim was to show that rats drank less of the same solution and exhibited fewer clusters than they did of the other solution, and that they reduced licking more rapidly to the same than the other solution. Experiments 2 and 3 followed the initial drinking bout with an injection of either FG 7142 or vehicle in order to assess the effects of the drug on intake and the size of the clusters elicited by subsequent exposure to the recently ingested or the relatively novel solution. We expected that rats injected with FG 7142 would drink less of the other solution and show fewer clusters than rats injected with vehicle, that is, we expected the drug to reduce intake and the hedonic reactions elicited by the relatively novel solution.

2. Materials and methods

2.1. Subjects

Subjects were experimentally naïve male Wistar rats (*Rattus norvegicus*) in each experiment. They were obtained from a commercial supplier (Animal Resources Centre, Perth, Australia) and weighed between 450 and 550 g. They were housed eight per cage in plastic boxes (22 cm high × 65 cm long × 40 cm wide) located in a climate controlled colony room on a 12 h light (7.00 a.m.–7.00 p.m.)–dark cycle. Approximately 1 week after arrival rats were handled 2 min per day for four consecutive days. During this time lab chow and water were continuously available. Experimentation was approved by the Animal Ethics Committee of The University of New South Wales and conducted in accordance with the National Institutes of Health guidelines.

2.2. Apparatus

The apparatus consisted in four chambers, each measuring 20 cm height × 21 cm length × 23 cm width. Each chamber was located within a sound and light attenuating shell. The walls and lid of a chamber were made of Perspex and the floor consisted of stainless steel rods (4 mm in diameter) spaced 1 cm apart. The front wall of a chamber contained a circular aperture (1.5 cm diameter) behind which was a drinking tube located outside the chamber. Rats contacted the drinking spout by inserting their tongue through the aperture. The drinking spout was fitted with a circuit connected to a computer which recorded licks.

2.3. Solutions and drugs

Two solutions were used. One consisted in a 0.05% sucrose solution, while the other consisted in a mixture of vanilla flavored ensure (Brand Name) and water (approximately 52 g powder per 130 ml water). Ensure powder provides (per 100 g) energy in the form of 14 g fat, 59.8 g carbohydrates and 16 g protein (437 calories/100 g). Sucrose (per 100 g) provides energy in the form of 100 g carbohydrates and 100 g sugars (407 calories/100 g). FG 7142 was used at a concentration of 10 mg/ml and was suspended in sterile isotonic saline (0.9%, w/v) using 1 drop of Tween 80 per 5 ml of saline. Vehicle was composed of isotonic saline plus Tween 80. FG 7142 and vehicle were administered by subcutaneous injection into the dorsal region of the neck in a volume of 1.0 ml/kg.

2.4. Familiarization

Rats were adapted to a fluid deprivation schedule which consisted in 1 h access each day to water in their home cages. This schedule remained in force throughout the experiment. Chow was always available in the home cages. Rats received alternating exposures to the sucrose and ensure across four days. There was one 30 min exposure each day.

2.5. Data collection and statistical analyses

The test data consisted in intake and licks. Bursts of licks were classified as runs separated by intervals ≤250 ms and bursts separated by a pause >250 and <500 ms were classified as a cluster. Bursts separated by a pause >500 ms were classified as an inter cluster pause. The mean number of licks per 10 s was calculated for each rat across the first four minutes of test to allow an analysis of licking rate. Data were analyzed by means of a planned, orthogonal contrast procedure controlling per contrast error rate [9] or, where appropriate, by post hoc paired sample *t* tests. Significance was set at $\alpha = 0.05$.

2.6. Experimental design

2.6.1. Experiment 1

The aim of this experiment was to demonstrate sensory-specific satiety. Rats were randomly allocated to four groups ($n = 8$). They received a 30 min exposure (session 1) to either sucrose or ensure. They were then returned to their home cages for a 30 min recess. Following recess, rats were returned to the chambers for a 10 min test session where they received either the same (sucrose–sucrose and ensure–ensure) or the other (sucrose–ensure and ensure–sucrose) solution.

2.6.2. Experiment 2

The aim of this experiment was to study the effects of FG 7142 on sensory-specific satiety. The design consisted in exposing rats to either sucrose or ensure on session 1. Then half of the rats were tested with the same solution (sucrose–sucrose and ensure–ensure) and the remainder with the other solution (sucrose–ensure and ensure–sucrose). Half of the rats within each group were tested first under the drug and then under vehicle while the reverse was the case for the remaining rats in each group. Following exposure to the solution (sucrose or ensure) on session 1, rats were returned to the home cages for 30 min and then returned to the chambers for test. Half of the rats were injected with FG 7142 and the remainder with vehicle 15 min before test. Testing involved rats either receiving the same solution ($n = 16$) as consumed during session 1 or the other solution ($n = 16$). The test session was 10 min in duration. Rats spent the following day in their home cages and then received a second test session. This was identical to the first (exposure followed 30 min later by test), except that subjects in each group previously injected with vehicle now received FG 7142, and subjects injected with FG 7142 received vehicle.

2.6.3. Experiment 3

The aim of this experiment was to replicate the effects of FG 7142 on sensory-specific satiety. Rats received two tests. On session 1 of each test day, rats were exposed to either sucrose ($n = 16$) or ensure ($n = 16$). Then (15 min later) half of the rats in each condition were injected with FG 7142 and the remainder with vehicle. All rats were tested 15 min later. Testing consisted in presentation of one solution for 10 min. This solution was either the same solution as that drank on session 1 or it was the other solution. This solution was then removed and immediately replaced with the other solution for an additional 10 min test. Rats spent the following day in their home cages. One day later, rats received a second test, identical to the first except that rats who previously received vehicle now received FG 7142 and vice versa. Thus, on each test, half of the rats first drank sucrose and 30 min later drank either sucrose followed immediately by ensure or they drank ensure followed by sucrose; the remainder first drank ensure and then 30 min later drank either ensure followed immediately by sucrose or they drank sucrose followed immediately by ensure. On the first test, half of the rats were injected with vehicle after session 1 while the remainder were injected with FG 7142, while on the second test, the vehicle injected rats were now injected with FG 7142 and vice versa.

3. Results

3.1. Experiment 1

The aim of this experiment was to demonstrate sensory-specific satiety. Rats were exposed to a solution (sucrose or ensure) and then tested with that or the other solution. The mean intakes of sucrose and ensure on the initial exposure were 18.6 ml (range 16–23 ml) and 19.4 ml (range 17–25 ml), respectively. Fig. 1 shows the test results. The upper panel shows the intake (Fig. 1A), clusters (Fig. 1B), and licks per cluster (Fig. 1C). Intake of the same solution was significantly less than of the other solution $F(1, 28) = 35.9$, p