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HPA axis dampening by limited sucrose intake: Reward frequency vs. caloric consumption

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ABSTRACT

Individuals often cope with stress by consuming calorically-dense, highly-palatable 'comfort' foods. The present work explores the stress-relieving properties of palatable foods in a rat model of limited sucrose intake. In this model, adult male rats with free access to chow and water are given additional access to a small amount of sucrose drink (or water as a control). A history of such limited sucrose intake reduces the collective (HPA axis, sympathetic, and behavioral-anxiety) stress response. Moreover, the stress-dampening by sucrose appears to be mediated primarily by its rewarding properties, since beneficial effects are reproduced by the noncaloric sweetener saccharin but not oral intragastric gavage of sucrose. The present work uses an alternate strategy to address the hypothesis that the rewarding properties of sucrose mediate its stress-dampening. This work varies the duration, frequency, and/or volume of sucrose and assesses the ability to attenuate HPA axis stress responses. The data indicate that HPA-dampening is optimal with a greater duration and/or frequency of sucrose, whereas increasing the volume of sucrose consumed is without effect. This finding suggests that the primary factor mediating stress-dampening is the number/rate of reward (i.e., sucrose) exposures, rather than the total sucrose calories consumed. Collectively, these data support the hypothesis that stress relief by limited palatable food intake is mediated primarily by its hedonic/rewarding properties. Moreover, the results support the contention that naturally rewarding behaviors are a physiological means to produce stress relief.

1. Introduction

Obesity is becoming increasingly prevalent and places a significant toll on individual and public health [1]. Among the factors linked with the obesity epidemic is the easy availability of palatable, calorically-dense foods, and an ever-escalating exposure to perceived stress [2–4]. When under stress, humans and rodents increase palatable food consumption [4–7], and the term 'comfort food' is commonly used to refer to the potential stress-relieving properties of certain foods (particularly calorically-dense foods containing high amounts of carbohydrates and/or fats). Indeed, palatable 'comfort' food intake in humans is linked with improved emotional states [8] and a high-carbohydrate diet is associated with reduced resting and stress-evoked cortisol levels [9–12]. Investigation of the stress-relieving properties of palatable 'comfort' foods in rodent models can provide potential novel strategies for intervening to prevent or curtail increasing rates of obesity and other metabolic disorders.

Rodents given free access to palatable foods (e.g., sucrose and/or lard) have attenuated HPA axis responses to stress [13–15]. These rats consume a large proportion of their daily calories as palatable foods (30–55%), resulting in a dramatically decreased (30–45%) intake of chow [7,13–16] and increased body weight and/or adiposity [7,16]. The marked decrease in chow intake and increased adiposity may themselves affect the HPA axis, thereby confounding interpretations of the effects of the food itself. Thus, we recently developed a model of limited sucrose intake in order to explore the mechanisms of stress-relief by palatable foods. In this model, rats with free access to food and water are given additional brief twice-daily access to up to 4 ml of 30% sucrose (vs. water as a control). Sucrose-drinking rats rapidly learn to drink the full amount of sucrose, and decrease their chow intake modestly (~10%) so that there is no effect on either body weight or fat depot weights [17]. Thus, this intake model provides the opportunity to assess stress responses in rats with a clamped limited sucrose intake (to avoid introducing additional variability in the amount consumed), thereby obviating potential confounds of large-scale reductions in chow intake or increases in body weight and/or adiposity.

In this limited intake model, sucrose reduces the collective (HPA axis, sympathetic, and behavioral-anxiety) response to stress [17,18]. Moreover, the stress-dampening by sucrose appears to be mediated primarily by its hedonic/rewarding properties, since the noncaloric sweetener saccharin reproduces the effect, and oral intragastric gavage of sucrose does not [17,18]. In addition, stress responses are similarly reduced in male rats that are given limited access to a sexually-receptive female rat, further supporting the idea that natural rewards (e.g., highly palatable foods or sexual activity) provide stress-dampening [18]. The present work

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provides an alternate strategy to address the hypothesis that the stress relief provided by sucrose is mediated by its rewarding properties. It comprises a parametric analysis of how altering sucrose (1) duration, (2) frequency, and (3) volume, affects its ability to produce HPA stress-dampening. Based on our hypothesis, we predict that the number and/or frequency of reward (i.e., sucrose) exposures rather than the sucrose volume (reflecting calories and macronutrient content) will be the most critical factors in determining stress relief.

2. Materials and methods

2.1. Animals

Adult male Long–Evans rats (~200–-225 g) were supplied by Harlan Labs (Indianapolis, IN). Rats were single-housed on a 12 h–12 h light cycle (lights on at 06:00 h) in a temperature and humidity-controlled housing facility with *ad libitum* access to normal chow (LM-485, Harlan Teklad) and water. Upon arrival, rats acclimated to the housing facilities for at least 1 week prior to the onset of experiments. All procedures were approved by the University of Cincinnati Animal Care and Use Committee.

2.2. Limited sucrose paradigm

Rats with free access to water and normal chow were given additional twice daily (at approximately 10:00 and 15:00 h) access to 4 ml of sucrose (30%; Sigma-Aldrich Co., St. Louis, MO) or water, and the volume consumed was recorded. A relatively small maximal volume of drink intake (4 ml/session) was selected to ensure that sucrose rats would reliably drink the full volume, thereby minimizing variations in the amount consumed as a factor contributing to increased variability of effects. Body weight and chow intake were also monitored. In this paradigm, sucrose does not affect body weight gain, nor the weights of any individual fat depots [17].

2.3. Restraint stress and plasma hormone measurement

On the morning (between ~08:00–12:00 h) following completion of the palatable drink paradigm, rats did not receive their respective drink solutions and were given a novel 20-min restraint stress challenge. Rats were placed into well-ventilated restraint tubes and 0-min tail clip blood samples (200 μl) were quickly collected into chilled tubes containing EDTA. The 0-min sample was completed in less than 3 min from first handling each rat's cage, thereby ensuring plasma ACTH and corticosterone levels that were reflective of the basal, unstressed state [19]. Rats remained in the restrainers for 20 min, with a second tail blood collection occurring immediately prior to their removal from the restraint tubes (i.e., 20-min after the onset of restraint). At 40 and 60 min after the initiation of restraint, the rats were briefly returned to the restraint tubes (<3 min) for collection of 40- and 60-min blood samples. It took less than 3 min to collect each post-stress blood sample. Post-stress sampling time points were chosen to optimize the assessment of the plasma corticosterone response (since this is the primary effector hormone of the axis), realizing that these time points may not be ideal for assessment of the plasma ACTH response (i.e., they are likely after the peak ACTH response). Blood samples were centrifuged (3000 *g*, 15 min, 4 °C) and plasma was stored at −20 °C until measurement of immunoreactive ACTH and corticosterone concentrations by radioimmunoassay as described previously [20].

2.4. Experiment 1: Duration of sucrose paradigm

This experiment assessed whether varying the duration of the sucrose paradigm (i.e., 1, 2, or 4 weeks) affected the subsequent HPA-dampening. Rats ($n = 9–10$/group) were assigned to 1 of 6 treatment groups: water for days 1–28, sucrose for days 1–28, water for days 15–28, sucrose for days 15–28, water for days 22–28, or sucrose for days 22–28. The start date of the drink paradigm was staggered so that all rats received their restraint test at the same time (day 29) to minimize variability in the HPA response.

2.5. Experiment 2: Frequency and volume of sucrose

This experiment assessed whether varying the frequency and/or volume of sucrose affected the subsequent HPA-dampening. Rats ($n = 10–11$/group) were assigned to 1 of 6 treatment groups: twice daily exposure (maximum 4 ml/session, or 8 ml/d) to water or sucrose, once daily exposure (maximum 4 ml) to water or sucrose, or once daily exposure (maximum 8 ml) to water or sucrose. Rats in the once daily exposure groups were housed in an adjacent room to avoid the potential confound of witnessing the second sucrose presentation of the twice daily groups. Drink exposure occurred on days 1–14 and all rats received their restraint test on the morning of day 15.

2.6. Statistical analyses

Data are shown as means ± SEM. For comparisons of multiple groups, data were analyzed by ANOVA (two-way or three-way, as appropriate) with repeated measures, followed by protected Fisher's post-hoc analysis. For time course data of the hormonal response to stress, the variance is often non-homogenous; in these instances ANOVA was performed following square-root transformation of the data. Differences in % change of integrated (area-under-the-curve) plasma corticosterone between water and sucrose were analyzed by one-tailed t-test since they tested the *a priori* directional hypothesis of diminished responses by sucrose. Potential outliers were assessed using two different tests: 1) outliers were values that differed from the mean by more than 1.96 times the standard deviation, and 2) outliers were values that were below the lower quartile or above the upper quartile by more than 1.5 times the interquartile range [21]. A positive identification by both outlier tests was required before a value was removed from the analysis. Statistical significance was taken as $p \leq 0.05$.

3. Results

3.1. Experiment 1: Duration of sucrose paradigm

When rats with free access to chow and water were given twice daily additional access to up to 4 ml of 30% sucrose, they rapidly learned to drink the sucrose (Fig. 1A). Sucrose intake approached the maximum allowed by the fourth or fifth days of exposure and was maintained at near maximal levels for the duration of the paradigm. In contrast, rats given twice daily access to an additional 4 ml of water drank very little throughout the paradigm, as expected since they were not water-restricted (for each duration, there was a main effect of DRINK ($p<0.01$), TIME ($p<0.01$) and a DRINK × TIME interaction ($p<0.01$)).

Sucrose-drinking rats decreased their chow intake (Fig. 1B) throughout the experiment regardless of the duration of sucrose exposure (for each duration, there was a main effect of DRINK ($p<0.05$), no main effect of TIME and no DRINK × TIME interaction).

Body weight (Fig. 1C) increased throughout the study and was not altered regardless of the duration of sucrose exposure (and despite the fact that the 1 week sucrose group had a slightly higher body weight prior to their sucrose exposure) (for each duration, there was a significant main effect of TIME ($p<0.01$) and no effect of DRINK; there was a significant DRINK × TIME interaction ($p = 0.042$) for only the 1 week duration).

On the morning of day 29, the rats did not receive their sucrose (or water) and were instead given a novel restraint stress challenge. Restraint increased plasma ACTH levels at all post-stress time points (Fig. 2A). Post-restraint plasma ACTH was generally lower in the cohorts of rats receiving the drink paradigm for 1 or 2 weeks, and sucrose drink did not alter the stress response for any of the experiment durations (significant main

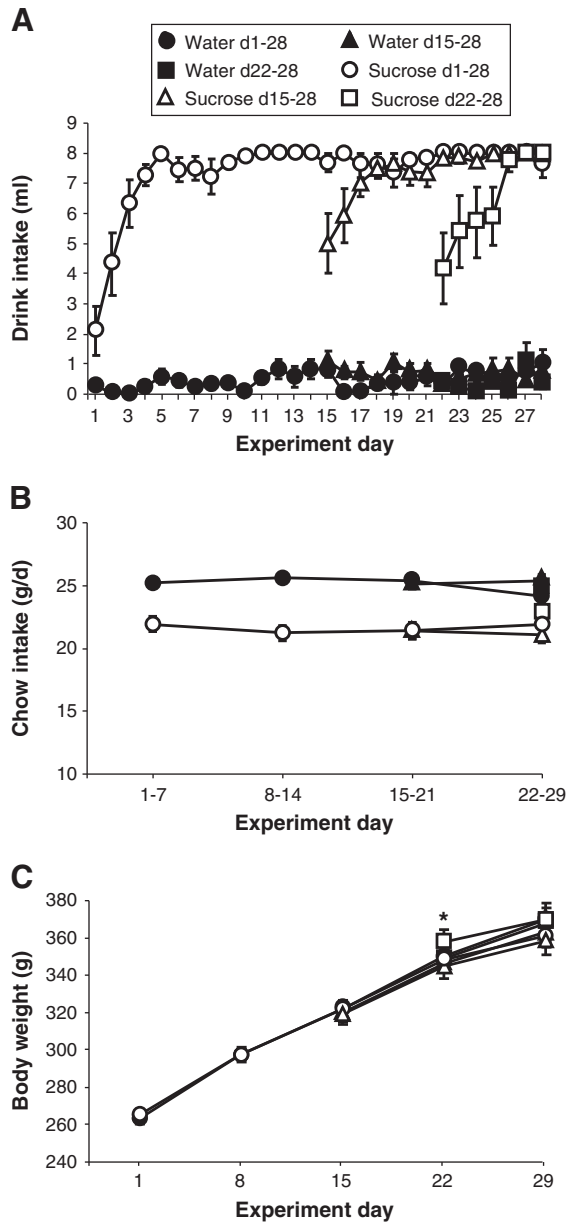

Fig. 1. For all durations of sucrose exposure, sucrose-drinking rats readily learned to drink the sucrose, and decreased their chow intake such that body weight was not altered. (A) Intake of rats given up to 4 ml of water or 30% sucrose twice daily for 7, 14, or 28 days. Not noted on figure: all sucrose values are greater than their respective water controls. (B) Chow intake for rats given water or sucrose drink for 7, 14, or 28 days. Not noted on figure: all sucrose values are less than their respective water controls. (C) Body weight of rats given water or sucrose drink for 7, 14, or 28 days. *$p<0.05$ vs. respective water control.

effects of DURATION ($p<0.01$) and TIME POST-STRESS ($p<0.01$), with no other main or interactive effects).

Restraint also increased plasma corticosterone levels at all post-stress time points (Fig. 2B). Post-restraint plasma corticosterone was generally higher in the cohorts of rats receiving the drink paradigm for 1 or 2 weeks. Importantly, sucrose decreased plasma corticosterone at 40 min (for 2 weeks sucrose duration) and/or 60 min (for 1, 2, and 4 weeks sucrose duration) post-restraint (significant main effects of DURATION ($p=0.01$), DRINK ($p=0.03$), and TIME POST-STRESS ($p<0.01$), with significant DURATION×TIME POST-STRESS ($p<0.01$) and DRINK×TIME POST-STRESS ($p<0.01$) interactions). Moreover, the integrated plasma corticosterone response to restraint (Fig. 3) was significantly reduced by sucrose only after 2 ($p=0.047$) and 4 ($p=0.038$) weeks of exposure.

3.2. Experiment 2: Frequency and volume of sucrose

As seen in Experiment 1, the rats rapidly learned to drink the sucrose (Fig. 4A). Sucrose intake approached the maximum allowed (either 4 or 8 ml/day) by the fourth or fifth day of exposure, and was maintained at near maximal levels for the duration of the paradigm, regardless of the sucrose frequency and volume. As previously mentioned, the rats given water drank very little throughout the paradigm (there were significant main effects of DRINK ($p<0.01$), PARADIGM ($p<0.01$) and TIME ($p<0.01$) and significant interactions between DRINK×PARADIGM ($p<0.01$), DRINK×TIME ($p<0.01$), and DRINK×PARADIGM×TIME ($p<0.01$)).

Sucrose-drinking rats decreased their chow intake (Fig. 4B) throughout the experiment. This reduction was most pronounced in the groups receiving 8 ml of sucrose per day, regardless of whether this intake spanned one or two daily sessions (there were significant main effects of DRINK ($p<0.01$) and PARADIGM ($p=0.05$) and a significant PARADIGM×TIME interaction ($p=0.026$), with no other main or interactive effects).

Body weight (Fig. 4C) increased throughout the study and was not altered regardless of the frequency and volume of sucrose (there was a significant main effect of TIME ($p<0.01$) and no other main or interactive effects).

Restraint stress increased plasma corticosterone levels at all post-stress time points (Fig. 5A). Sucrose decreased post-stress plasma corticosterone levels regardless of sucrose frequency and volume. More specifically, post-restraint plasma corticosterone was reduced by twice daily sucrose at 60 min, by once daily 4 ml of sucrose at 20 and 60 min, and by once daily 8 ml of sucrose at 40 and 60 min. However, the post-restraint plasma corticosterone levels of sucrose-drinking rats was higher in the groups receiving sucrose once daily (either 4 or 8 ml) compared to those receiving sucrose twice daily at 20 and/or 60 min after stress. These results suggest that the sucrose was less effective at suppressing the HPA response when given once daily (significant main effects of DRINK ($p=0.010$) and TIME POST-STRESS ($p<0.01$), with significant interactions between PARADIGM×TIME POST-STRESS ($p=0.014$) and DRINK×PARADIGM×TIME POST-STRESS ($p=0.021$)). Consistent with this finding, the integrated plasma corticosterone response to restraint (Fig. 5B) was significantly reduced only after twice daily sucrose availability.

4. Discussion

4.1. Summary

Ad libitum fed rats that were given additional access to limited amounts of sucrose rapidly learned to drink the sucrose in amounts approaching the maximum permitted, regardless of paradigm duration, frequency or volume. Sucrose-drinking rats also decreased their chow intake in amounts roughly isocaloric with the calories provided by the sucrose, regardless of paradigm duration, frequency or volume. As a result, sucrose had no effect on body weight in any administration paradigm. Importantly, sucrose drink consistently reduced the plasma corticosterone levels at 20, 40 and/or 60 min post-restraint. Moreover, analysis of the integrated plasma corticosterone response to restraint revealed that maximal HPA dampening required (1) at least 2 weeks of sucrose exposure, and (2) twice daily frequency.

4.2. Potential mechanisms of HPA-dampening by sucrose

In the present work, as well as in previous studies [17,18], sucrose intake predominantly affected the plasma corticosterone, and not the

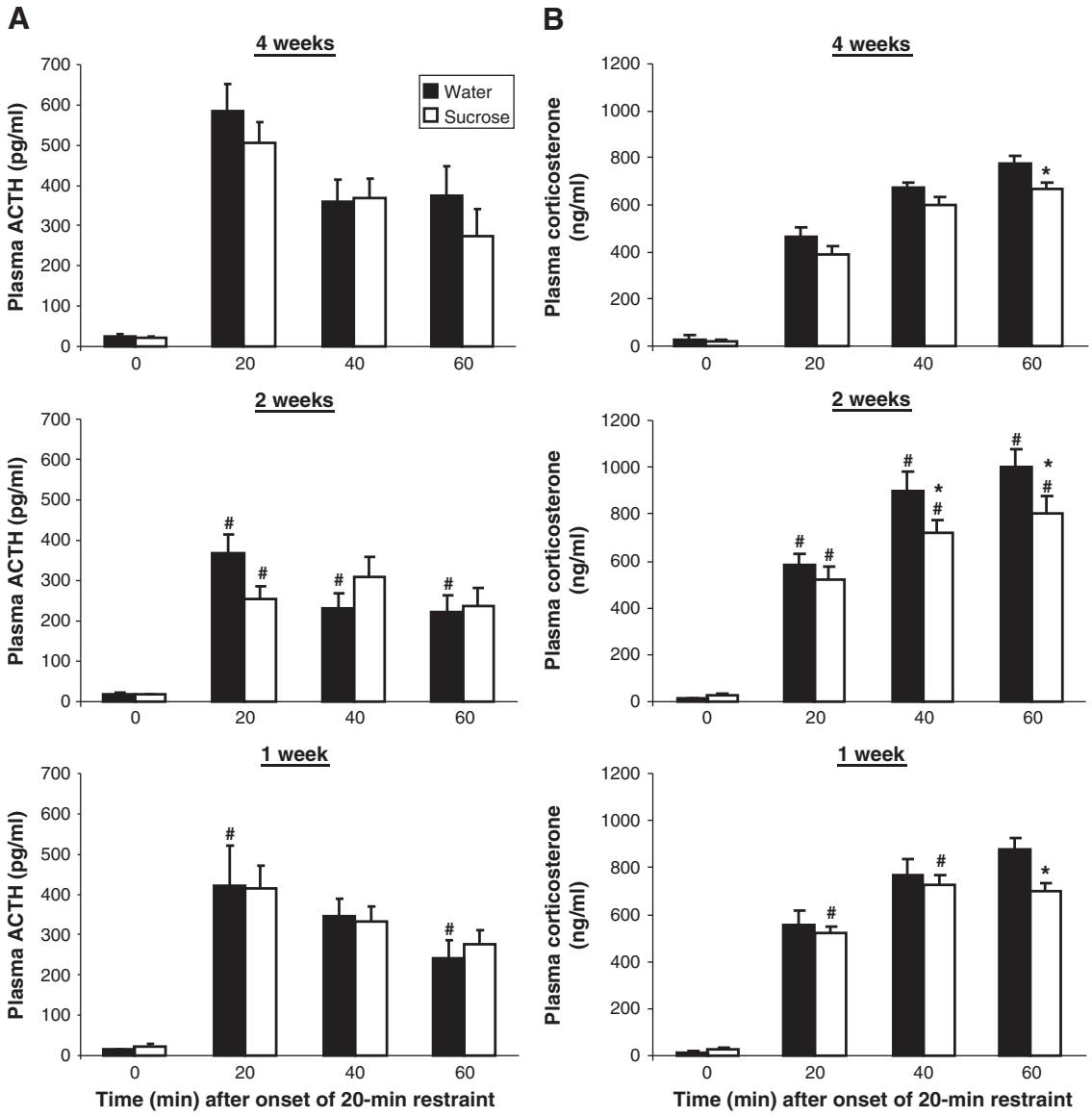

Fig. 2. Sucrose decreased the plasma corticosterone, but not the plasma ACTH, response to restraint stress. (A) The time course of restraint-stress-induced plasma ACTH for rats receiving sucrose or water twice daily for 4 (*top*), 2 (*middle*) or 1 (*bottom*) week. (B) The time course of restraint-stress-induced plasma corticosterone for rats receiving sucrose or water twice daily for 4 (*top*), 2 (*middle*) or 1 (*bottom*) week. Please note that for each hormone, the statistics depicted on the figure resulted from a three-way ANOVA comparing DRINK, DURATION, and TIME POST-STRESS. Not noted on figure: all values at 20, 40, and 60 min are greater than 0 min. #$p<0.05$ vs.4 weeks, *$p<0.05$ vs. water.

plasma ACTH, response to restraint. Such dissociations between post-stress plasma ACTH and corticosterone are common [7,22–24], and could indicate that sucrose acts to decrease adrenal sensitivity to ACTH. However, our previous work shows that adrenal responsivity to ACTH is not altered by limited sucrose intake [18]. Moreover, limited sucrose (and saccharin) intake decreases the expression of CRH mRNA in the PVN (the primarily central regulator of the HPA axis) [17]. In addition, neural signaling in the basolateral amygdala, a key reward- and stress-regulatory brain region, is necessary for sucrose-mediated stress dampening [18]. Collectively, these results demonstrate that sucrose acts, at least in part, at central sites of HPA axis regulation. Thus, the observed dissociation between post-stress plasma ACTH and corticosterone is most likely due to the timing of sample collection, which was optimized for the detection of post-stress corticosterone, and/or differences between bioactive and immunoreactive ACTH [25].

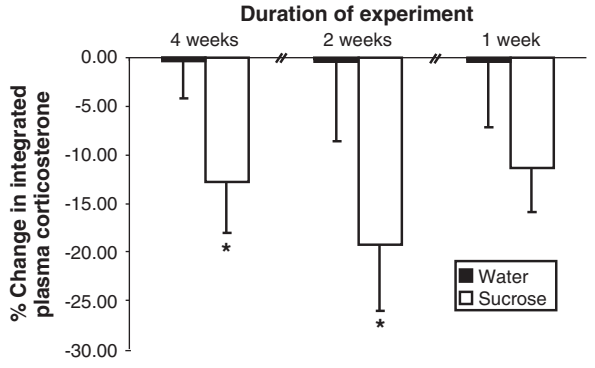

Fig. 3. At least 2 weeks of twice daily sucrose exposure was required to reduce the integrated plasma corticosterone response to restraint. *$p<0.05$ vs. water.

4.3. Role of sucrose reward vs. calories

Highly palatable 'comfort' foods have multiple attributes that can be crudely divided into two categories: metabolic properties (e.g., calories, macronutrient composition) and non-metabolic properties (e.g., taste,

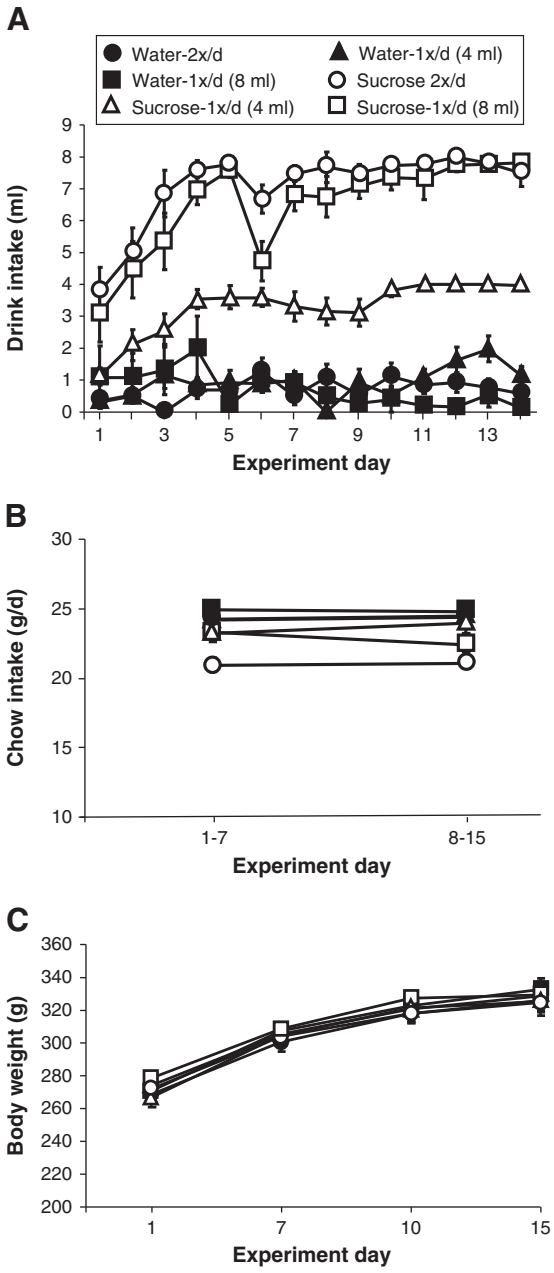

Fig. 4. For all frequencies and volumes of sucrose, sucrose-drinking rats readily learned to drink the sucrose, and decreased their chow intake such that body weight was not altered. (A) Intake of rats given twice daily (up to 4 ml/session with 8 ml/day maximum) sucrose or water, or once daily (up to either 4 ml/day or 8 ml/day) water or sucrose for 14 days. Not noted on figure: (1) all sucrose values are greater than their respective water controls except for the 'once daily 4 ml' cohort on experiment day 1; and (2) the sucrose intake of the 'once daily 4 ml' group is less than the other sucrose groups on all experimental days. (B) Chow intake for rats given twice daily (8 ml/day) or once daily (either 4 ml/day or 8 ml/day) water or sucrose. Not noted on figure: all sucrose values are less than their respective water controls except for the 'once daily 4 ml' cohort at experiment days 8–15. (C) Body weight of rats given twice daily (8 ml/day) or once daily (either 4 ml/day or 8 ml/day) water or sucrose.

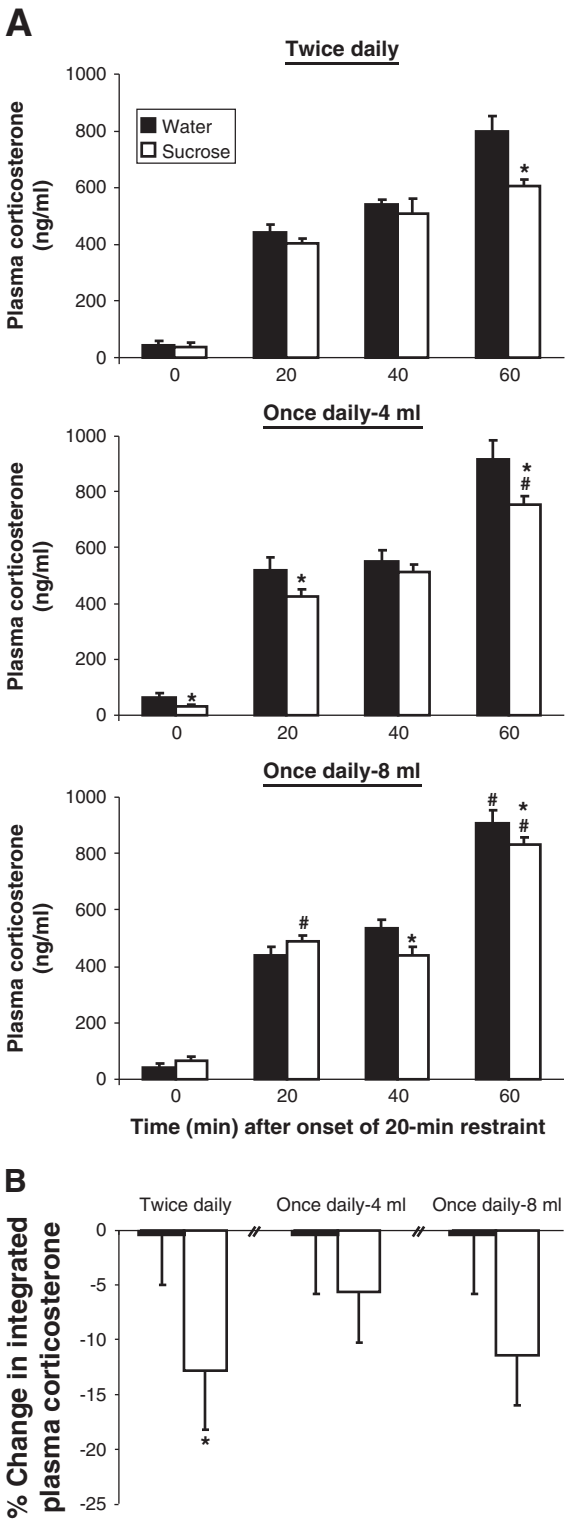

Fig. 5. Sucrose decreased the plasma corticosterone response to restraint stress, and twice daily sucrose was more effective than once daily sucrose. (A) The time course of restraint-stress-induced plasma corticosterone for rats receiving 4 ml sucrose or water twice daily (*top*), 4 ml of sucrose or water once daily (*middle*), or 8 ml of sucrose or water once daily (*bottom*). The statistics depicted on the figure resulted from a three-way ANOVA comparing DRINK, PARADIGM, and TIME POST-STRESS. Not noted on figure: all values at 20, 40, and 60 min are greater than 0 min. #$p<0.05$ vs. twice daily, *$p<0.05$ vs. water. (B) Twice daily sucrose exposure was required to reduce the integrated plasma corticosterone response to restraint. *$p<0.05$ vs. water.

hedonics, and reward). Previous work indicates that the stress relief provided by limited palatable food intake is largely mediating by its hedonic/rewarding properties. For example, the noncaloric sweetener saccharin is sufficient to produce HPA axis dampening, as are alternative naturally rewarding behaviors (e.g., sexual activity) [17,18]. Oral intragastric gavage of sucrose is ineffective in reducing stress responses, suggesting that calories and other post-ingestive properties of sucrose (including the ensuing neural and hormonal responses) are not sufficient to dampen HPA axis activation [18]. Moreover, the basolateral amygdala, a region that is an integral part of brain reward circuitry, is required for stress-dampening by sucrose [18]. Collectively, these results strongly

suggest that stress-dampening by sucrose is primarily mediated by its hedonic/rewarding properties.

The present results support this contention. Maximum sucrose reward is likely obtained by giving numerous exposures to a small volume of the 30% sucrose solution. For instance, activation of the reward system occurs with the onset of a palatable meal, or with environmental cues that predict a palatable meal [26–30]. This initial activation then decreases throughout the meal [28,29,31], suggesting that increasing the volume (i.e., size and duration) of a sucrose meal will produce minimal increases in the total amount of reward activation. Moreover, in sham-drinking rats, activation of the reward system appears to be related primarily to the concentration of sucrose consumed, rather than its volume [32,33]. Taken together, these findings suggest that doubling the frequency of 30% sucrose exposure (from once to twice daily) greatly increased the total reward experienced, whereas doubling the volume of sucrose consumed (from 4 to 8 ml) produced minimal increases in its reward value. In contrast, maximum calories and macronutrients would be obtained by the consumption of larger volumes of sucrose. In the present work, once daily sucrose was less effective than twice daily even when the total amount of sucrose consumed each day was equivalent (both 8 ml), demonstrating that a higher number of exposures is more important than the total calories ingested. Moreover, once daily access to 8 ml sucrose was not significantly more effective than 4 ml, suggesting that increasing the calories ingested was not sufficient to increase stress-dampening. Taken together, these results support the hypothesis that stress-dampening is mediated primarily by the rewarding properties of palatable foods. In addition, sucrose calories (and/or macronutrients) may contribute to the rewarding properties of the sucrose [34,35]; this is reflected by the fact that 8 ml sucrose given once daily appeared to be slightly (although not significantly) more efficacious than the 4 ml once daily dose. It is possible that the metabolic properties of sucrose (e.g., calories and macronutrients) may contribute to the stress relief via their direct (e.g., central glucose-sensing neurons) and indirect (e.g., neural and hormonal responses such as increased circulating insulin) actions on stress-regulatory sites in the brain; however, these effects alone are likely not sufficient since oral intragastric gavage of sucrose does not provide stress relief [18].

4.4. Physiological relevance

The presently described stress dampening by limited palatable food intake is likely of significant physiological relevance. Palatable drink consistently reduced the HPA axis response to stress by approximately 10–20%. This attenuation may seem relatively modest; however, it likely provides a cumulative physiological impact over long periods of time. For example, prolonged, subtle changes in HPA axis tone are associated with diminished bone density and cognitive function in humans [36,37].

Collectively, these findings indicate that 'comfort' food intake is a physiological means to provide stress relief. Moreover, the results support the contention that the rewarding properties of palatable foods contribute to the stress relief. The work provides a clearer understanding of the motivation to consume palatable foods during times of stress and may influence therapeutic strategies for the prevention and/or treatment of obesity and other stress-related disorders.

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