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Individual Differences in Sucrose Intake Predict Behavioral Reactivity in Rodent Models of Anxiety

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DESOUSA, N. J., G. R. WUNDERLICH, C. DE CABO AND F. J. VACCARINO. *Individual differences in sucrose intake predict behavioral reactivity in rodent models of anxiety.* PHARMACOL BIOCHEM BEHAV **60**(4) 841–846, 1998.— We have previously shown that individual differences in oral sucrose consumption are predictive of behavioral reactivity of rats in the elevated plus-maze (EPM). The present experiments were designed to replicate the EPM results and to extend them to another animal model of anxiety, the acoustic startle reflex (ASR) paradigm. In two experiments, sucrose consumption was assessed in separate groups of rats across eight daily 1-h feeding sessions. Animals were designated as either low (LSF) or high sucrose feeders (HSF) based on a median split of their sucrose intake on the final test day. Following this assay, animals were tested in the EPM in Experiment 1, and in the ASR paradigm in Experiment 2. Results from Experiment 1 replicated our previous findings and showed that the percentage of time spent on, and entries into, open arms was significantly lower in LSF than HSF. Further, results from Experiment 2 revealed a significantly augmented startle response to acoustic stimuli (94–108 dB SPL) in LSF compared to HSF. These data provide converging evidence to support the notion that individual differences in baseline levels of oral sucrose consumption are predictive of anxious behaviors in rats. © 1998 Elsevier Science Inc.

Individual differences Sucrose Plus-maze Acoustic startle Approach Avoidance Anxiety

RATS demonstrate considerable variability in their propensity to ingest a sweet substance such as sucrose (7,9,32–37). Over the past several years, a number of studies from our laboratory have demonstrated that individual variability in sucrose feeding is predictive of individual differences in other behaviors sharing an appetitive profile. For example, we have shown that the behavioral effects of psychostimulants in sucrose feeding and exploratory locomotor activity paradigms are blunted in low sucrose feeding animals (LSF), relative to high sucrose feeders (HSF) (32,34–36). In line with these finding, it has been reported that sucrose intake also predicts the acquisition of intravenous psychostimulant self-administration, such that LSF acquire this behavior less readily than do HSF (9). Further, LSF demonstrate blunted self-administration levels, relative to HSF, across a wide range of psychostimulant doses. Together, these data support the hypothesis that individual differences in sucrose intake may be predictive of other positively motivated behaviors (40). Specifically, these studies suggest that HSF, relative to LSF, may be characterized by an exaggerated tendency to engage in behaviors associated with investigation, approach, and reinforcement.

Although attention has focused on individual differences in sucrose intake as a predictor of behaviors characterized by positive motivational states, other types of behaviors have received much less attention. We have recently undertaken studies aimed at examining the expression of negatively motivated behaviors. Unlike the sucrose feeding, exploratory locomotor activity, and self-administration paradigms, the elevated plus-maze (EPM) paradigm appears to measure fear-motivated avoidance behavior (15,27). During EPM testing,

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animals are exposed to two open (unwalled), and two closed (walled) arms. Studies have shown that rats will actively avoid the open arms, relative to closed arms, due to their fear of open spaces (39). In this paradigm we have demonstrated that LSF show greater fear-like behavior, as evidenced by reduced open-arm exploration relative to HSF (7). This result suggests that in addition to demonstrating decreased expression of behaviors associated with approach, LSF also demonstrate heightened avoidance behavior relative to HSF.

Consistent with their effects in other paradigms measuring avoidance behavior (12), drugs with an anxiolytic profile increase exploration of open, relative to closed, arms in the EPM in rats (28). Conversely, anxiogenic manipulations decrease open-arm exploration. As a result, the EPM has been proposed as an animal model of anxiety based on the interplay between exploration and avoidance. The acoustic startle reflex (ASR) paradigm is another model that has been used to study processes underlying anxiety. In this paradigm, animals are presented with a sudden intense acoustic stimulus that causes a defensive startle reflex consisting of the sequential contraction of muscles along the length of the body. Manipulations consistent with increased or decreased fear or anxiety have been shown to respectively potentiate or inhibit startle responses in both humans (2,4,8,14,43) and laboratory animals (6,11,17,19,30,47). As such, the ASR paradigm has been proposed as an exploration-independent animal model of anxiety.

If the behavioral differences in reactivity to the EPM observed between LSF and HSF are related to individual differences in anxiety, these groups should also differ in animal models of anxiety that are not based on exploration and avoidance. To address this issue, the present set of experiments were designed to replicate the original EPM findings and to test the general hypothesis that individual differences in oral sucrose intake are predictive of anxiety-like behaviors in other behavioral measures such as the ASR.

METHOD

This research was conducted with due regard for the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care and relevant University of Toronto policy.

Experiment 1: Sucrose Feeding and Plus-Maze Reactivity

Subjects. Male Wistar rats (n = 21) purchased from Charles River, Canada, were used in Experiment 1. At the time of arrival rats, weighing 250–275 g, were housed individually in Plexiglas cages in a temperature-controlled (21 ± 1°C) colony room maintained on a 12 L:12 D cycle (lights off at 0700 h). Purina lab pellets and water were available in the home cages ad lib except as noted.

Apparatus

The EPM was constructed of black Plexiglas and consisted of two opposing open arms (10 × 50 cm) crossed at a 90° angle with two opposing closed arms (10 × 50 cm). The latter arms were enclosed by walls measuring 40 cm in height. Connecting these arms was a center area measuring 10 × 10 cm. The floor of the maze was painted with a "speckled stone" paint producing a rough surface to facilitate grip. The maze was situated in a dimly lit room supported by a stand that elevated it 60 cm above the floor. A camera was mounted above the maze and connected to a video monitor and cassette recorder in an adjoining room where an observer could quantify an animal's behavior.

Procedure

The initial experiment demonstrating that LSF and HSF differed in their behavioral reactivity to the EPM was conducted during the animals' light cycle (7). Consistent with previous studies (13), testing during this period produced low levels of open-arm exploration and reduced variability. To increase open-arm exploration levels, the present experiment was conducted entirely during the animals' dark phase. Previous results show that while dark-cycle testing results in greater levels of baseline feeding, the relative difference between LSF and HSF is maintained across the circadian cycle (32).

Feeding phase. Food pellets were removed from the home cage and rats were presented with two preweighed stainless steel cups (8 cm diam. × 4 cm deep), each containing either granulated sucrose or powdered chow, for a period of 1 h. At the end of this session, food cups were removed and weighed, and animals were again allowed ad lib access to fresh chow pellets for the remaining 23 h. This procedure was repeated over 8 days, with the exception that on the final test day animals received an intraperitoneal injection of saline (1 ml/kg) immediately before the presentation of sucrose and chow. Animals were divided into LSF and HSF groups based on a median split of day 8 intake. As a feeding control, rats were also divided in low (LCF) and high chow feeders (HCF) based on whether chow was consumed during day 8 testing.

Plus-maze testing phase. Following the feeding assay, rats were tested for their behavioral reactivity to the EPM. Rats were removed from their home cage, placed in a carrying cage, and transported to a holding room for a period of 10 min. Following this period animals were then placed in the EPM and monitored by video camera for a period of 5 min. An observer blind to group designation quantified the duration of time spent on, and entries into, open and closed arms.

Statistical Analysis

Behavior in the EPM was assessed by measuring both the duration of time spent on open and closed arms, as well as the number of entries into the open and closed arms. These raw data were used to calculate percent open-arm duration and percent open-arm entry scores (open/[open + closed]), which were analyzed by single-factor (group) between-subjects analysis of variance (ANOVA).

Experiment 2: Sucrose Feeding and Acoustic Startle Reactivity

Subjects. As in Experiment 1, male Wistar rats (n = 24) purchased from Charles River, Canada, were used. At the time of arrival rats, weighing 250–275 g, were housed individually in Plexiglas cages in a temperature-controlled (21 ± 1°C) colony room maintained on a 12 L:12 D cycle (lights on at 0700 h). Again, Purina lab pellets and water were available in the home cages ad lib except as noted.

Apparatus

Four ventilated and sound-attenuating ASR chambers (SR-LAB, San Diego Instruments, San Diego, CA) were used. Each startle chamber contained a stimulus package consisting of a dim house light, as well as a loudspeaker (approx. 25 cm from the animal) capable of generating background noise and acoustic startle stimuli. During testing, animals were confined to a Plexiglas cylinder (8 cm) that rested on a Plexiglas sensor platform. Each platform housed an accelerometer that sensed and transduced vertical displacement generated by the startle response. All stimulus parameters were

controlled, and startle data recorded, via an interface assembly (San Diego Instruments) and an IBM compatible PC in an adjoining room.

Procedure

Behavioral activity levels are greater during the rats' dark cycle than during their light cycle. Because increased activity levels may confound startle amplitude results (29,45), this experiment was conducted entirely during the animals' light cycle. As stated, circadian variables do not appear to differentially affect LSF and HSF (32).

Feeding phase. Assessment of sucrose and chow feeding was conducted as per Eexperiment 1 except as otherwise noted. This feeding assay produced separate groups of animals designated as either LSF or HSF, as well as LCF or HCF.

Acoustic startle testing phase. Following the feeding assay, rats were tested for their behavioral response in the ASR paradigm. Rats were removed from their home cage and transported via carrying cage to the ASR chambers. Before testing, animals were habituated to the startle apparatus for a period of 5 min. During this period, animals were exposed to a background 70 dB SPL white noise stimulus and dim house light that remained on throughout habituation and testing. Following habituation, animals were then exposed to 10 trials of 10 white noise stimuli (50 ms; 82, 83, 84, 85, 87, 90, 94, 100, 108, and 120 dB SPL). Within trials, the order of stimulus presentation was randomized on a fixed interval 12-s schedule. Startle amplitudes were recorded via a PC.

Statistical Analysis

In Experiment 2, individual acoustic startle responses were quantified by averaging 100 startle amplitude readings (arbitrary units) produced during the 100 ms period following stimulus onset. Due to heterogeneity of variance for mean startle responses across stimulus intensities, square-root (sqrt) transformations were performed on the raw startle amplitude scores (21). This transformed data was analyzed by mixed three-factor (group $\times$ intensity $\times$ trial) ANOVA, followed by a Newman–Keuls post hoc test.

RESULTS

Experiment 1

Feeding phase. Following 7 days of acquisition, animals (n = 21) were tested for their sucrose and chow intake following an intraperitoneal injection of saline. Examination of the feeding data revealed that animals consumed a greater amount of granulated sucrose (4.85 $\pm$ 0.47 g) than powdered chow (0.75 $\pm$ 0.34 g) over the 1-h test period. Analysis of the data showed that intake levels during this final test session were comparable to those during the previous 3 days of feeding acquisition. Based upon a median split of their sucrose intake levels on the final test day, rats were divided into LSF (n = 10; 3.22 $\pm$ 0.27 g) and HSF (n = 10; 6.48 $\pm$ 0.60 g) groups. A large number of rats did not consume chow and as a result animals were divided into LCF and HCF groups based on whether they did not consume chow (n = 12; 0 g), or consumed chow (n = 9; 1.74 $\pm$ 0.67 g), respectively. For the purposes of statistical testing, nine rats were chosen at random from the LCF group. This procedure was adopted to utilize the classic sum-of-squares formula (20,21,24). Visual inspection of EPM means (data not shown) confirmed that this smaller LCF group was representative of the larger LCF group.

EPM testing. Figures 1A and B show the percentage of time spent on open arms in the sucrose and chow feeding groups, respectively. As can be seen in Fig. 1A, LSF spent a lower percentage of time on open arms than HSF. On the other hand, LCF and HCF do not differ substantially in this measure, as evidenced in Fig. 1B. Figures 1C and D show the percentage of entries into open arms in both sucrose and chow groups. As shown in Fig. 1C, the percentage of entries into open arms was lower in LSF than HSF. However, LCF did not appear to differ form HCF, as evidenced in Fig. 1D.

Statistical analyses support this description of the data. Four single-factor between-subjects ANOVAs were conducted to examine the EPM response in the different feeding groups. Separate ANOVAs of the percentage of time spent on open arms showed a significant main effect of group in LSF and HSF, $F(1, 18) = 8.07$, $p < 0.01$, but not in LCF and HCF. Similarly, separate ANOVAs of the percentage of entries into open arms showed a significant group main effect in LSF and HSF, $F(1, 18) = 7.53$, $p < 0.05$, but not in LCF and HCF.

Experiment 2

Feeding phase. Sucrose and chow intake levels were collected for animals (n = 24) as per Experiment 1. As in the first experiment, animals consumed a greater amount of granulated sucrose (1.96 $\pm$ 0.24 g) than powdered chow (0.40 $\pm$ 0.21 g) over the 1-h test period. As in Experiment 1, intake levels during this final test session were comparable to those during

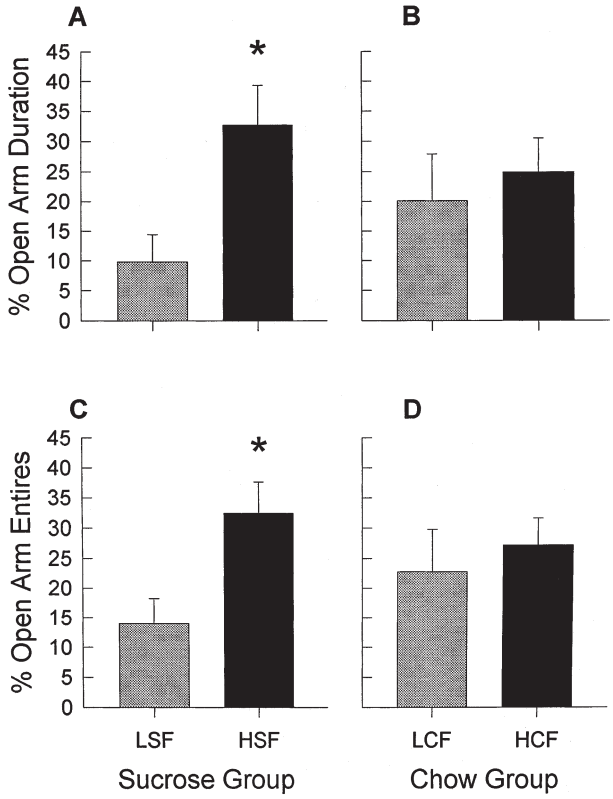

FIG. 1. The mean (±SEM) percentage of time spent on (A and B), and percentage of entries into (C and D), the open arms of the elevated plus maze over a 5-min test period in low and high oral sucrose (A and C) and chow (B and D) intake groups. *Significant group effect by one-way ANOVA ($p < 0.05$).

the previous 3 days of feeding acquisition. Consistent with previous results (32), intake levels were lower during light cycle testing (Experimemt 2) than during dark cycle testing (Experiment 1). Based upon a median split of their sucrose intake levels, rats were divided into LSF (n = 12; 1.03 ± 0.13 g) and HSF (n = 12; 2.89 ± 0.23 g) groups. Again, a number of rats did not consume chow and as a result animals were divided into LCF and HCF groups based on whether they did not consume chow (n = 18; 0 g), or consumed chow (n = 6; 1.58 ± 0.65 g), respectively. For the purposes of statistical testing, six animals were chosen at random from the LCF. Again, this procedure was adopted so that the classic sum-of-squares formula could be utilized (20,21,24). Examination of ASR means (data not shown) showed this smaller LCF group to be representative of the larger LCF group.

ASR testing. Figure 2A and B shows the sqrt transformed startle amplitude scores of sucrose and chow feeding groups, respectively. Although Fig. 2A shows that startle amplitude was greater in LSF than HSF across a number of startle intensities, Fig. 2B demonstrates that LCF did not differ from HCF.

Statistical analyses confirm this interpretation of the data. Two mixed three-factor ANOVAs (group × intensity × trial) were conducted to examine startle responses in the sucrose and chow feeding groups. ANOVA of the sqrt transformed startle amplitude scores of LSF and HSF showed significant main effects of group, $F(1, 22) = 10.08$, $p < 0.005$, and intensity $F(9, 198) = 64.21$, $p < 0.000001$, but not trial. For the intensity factor, Newman–Keuls post hoc tests of simple effects showed that the startle amplitude at lower intensities (82 and 83 dB SPL) differed significantly ($p < 0.05$) from startle amplitudes at higher intensities (90–120 dB SPL). The group × intensity interaction also reached significance, $F(9, 198) = 2.37$ $p < 0.05$, and post hoc analyses using the Newman–Keuls test demonstrated that LSF significantly ($p < 0.01$) differed from HSF across several stimulus intensities (94, 100, and 108 dB SPL). In addition, the intensity × trial interaction was significant, $F(81, 1782) = 1.44$, $p < 0.01$, and subsequent Newman–Keuls post hoc testing of simple effects showed that startle amplitude decreased significantly ($p < 0.0001$) across trials (i.e., 1 vs. 10) for stimuli at 120 dB SPL, but not for stimuli at lower intensities.

For the chow feeding groups, ANOVA (group × intensity × trial) of the sqrt transformed ASR scores showed a significant main effect of intensity, $F(9, 90) = 34.05$, $p < 0.000001$, but not group, or trial. Newman–Keuls post hoc testing showed that the startle amplitude at lower intensities (82 and 83 dB SPL) differed significantly ($p < 0.05$) from startle amplitudes at higher intensities (94–120 dB SPL). None of the interactions reached statistical significance.

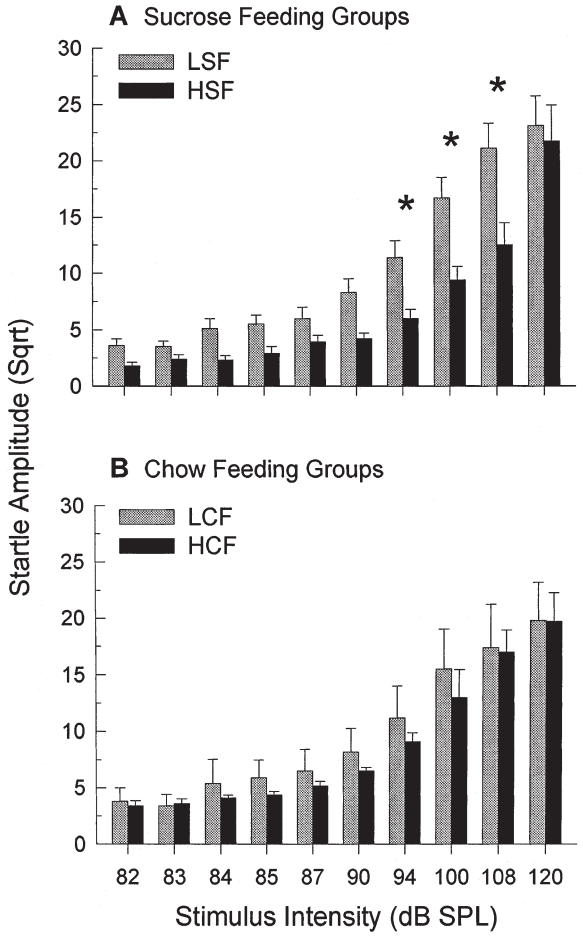

FIG. 2. The mean (±SEM) square-root transformed startle amplitude scores across 10 acoustic stimulus intensities in low and high oral sucrose (A) and chow (B) intake groups. *Significant by Newman–Keuls post hoc test ($p < 0.05$).

DISCUSSION

Results from Experiment 1 are consistent with previous results from our group (7). The findings demonstrate that the percentage of time spent on, and entries into, open arms of the EPM was significantly lower in rats designated as LSF than those designated as HSF. However, animals split into groups based on their chow intake did not demonstrate a similar effect. In Experiment 2, results showed that LSF demonstrated an augmented startle response to the presentation of acoustic stimuli (94, 100, or 108 dB SPL) in comparison to HSF. Again, this effect was not seen in groups based on their chow intake. Together, these results provide support for the hypothesis that individual differences in baseline levels of sucrose consumption are predictive of the degree to which animals express anxious behaviors.

Because acoustic startle is a reflex that is potentiated by anxiogenic manipulations such as the presentation of fear-conditioned stimuli (6,19), and panicogenic agents (11,47), the ASR paradigm has been proposed as an exploration-independent animal model of anxiety. Results from Experiment 2 showing that LSF were more reactive than HSF to mid, but not maximal, level intensity acoustic stimuli suggest a decreased threshold for LSFs' reactivity to anxiogenic stimuli. This ASR effect is consistent with EPM results from Experiment 1, as well as those from previous studies (7). Together, these results suggest that the differences between LSF and HSF may be more accurately captured by explanations based upon anxiety-related processes than by explanations based simply upon approach–avoidance mechanisms.

There exist at least three interpretations for the present results. One line of reasoning relates to the relationship between benzodiazepine (BDZ) action, anxiety, and ingestional behaviors. A second explanation relates to the potential involvement of dopamine (DA) mechanisms in sucrose feeding as well as emotional and anxiety-related behaviors. Finally, a third interpretation of the present results relates to neurochemical differences between LSF and HSF in cholecystoki-

nin (CCK) systems, which have recently been implicated in panic disorder and anxiety. Each of these potential mechanisms will be elaborated below.

Consistent with the anxiolytic effects of systemically administered BDZs, recent studies suggest that individual differences in endogenous benzodiazepine systems can be used to predict anxiety-like behaviors. Specifically, data show that high "anxious"-type rats demonstrating decreased time spent on, and entries into, the open arms of the EPM have significantly lower levels of BDZ binding in the brain than do their intermediate and low "anxiety" counterparts (16). These results suggest that low levels of endogenous BDZ activity are associated with high levels of anxiety. These data may provide interesting insights into the present results if one considers the growing body of literature that focuses on the effects of BDZ manipulations on ingestional behaviors (1,5). Several of these studies have reported that BDZs' enhance affective reactions to taste palatability in rats. For example, anxiolytic drugs such as diazepam and chlordiazepoxide potentiate feeding and hedonic taste reactivity (i.e., rhythmic tongue protrusions) to oral sucrose when injected intracerebroventricularly in rats (26). Together, these studies allow for the intriguing hypothesis that individual differences in BDZ systems may underlie the individual differences seen in both sucrose feeding and anxiety-like behavior in the present study. According to this BDZ hypothesis, LSF should demonstrate lower BDZ receptor densities than HSF. Decreased levels of BDZ activity should then result in lower sucrose intake due to blunted hedonic taste reactivity, and greater anxiety-like behavior due to compromised endogenous BDZ neurotransmission. This hypothesis remains to be tested.

A number of reports suggest the involvement of nucleus accumbens (NAcc) DA mechanisms in both sucrose feeding and anxiety (41). First, intra-NAcc DA agonist-stimulated food intake was shown to be sucrose specific when rats were presented with a choice of various sucrose/chow combinations (10,32). Second, a similar manipulation with a DA antagonist reduced intake volume of a sucrose solution that was matched by an increase in water intake in a two-bottle test (46). Third, individual differences in oral sucrose intake predict the degree of DA agonist-induced sucrose feeding (32,34,36), locomotor activity (35), self-administration (9), and NAcc-DA overflow as measured by in vivo microdialysis (33). Of relevance to the present results, DA systems may also be implicated in the modulation of anxiety-like behaviors. For example, DA systems have long been linked with positive affective or hedonic processes (22). Interestingly, a number of studies have highlighted the relationship between affective states and anxiety in humans (3,4,43,44). Together, these studies suggest that stimuli associated with positive or negative affect respectively reduce or potentiate measures of anxiety, such as startle, in humans. According to this idea, the differences in anxious behaviors seen in LSF and HSF in the present experiments may result from different affective responses to certain stimuli due to underlying individual differences in DA mechanisms. Although this idea remains to be tested in relation to individual differences in sucrose feeding, a number of preliminary behavioral studies have reported complex effects of DAergic agents in different animal models of anxiety (25,31,38).

In addition to DA, a number of results have implicated CCK mechanisms in the mediation of individual differences in oral sucrose intake as well as anxiety. Thus, both systemic and intra-NAcc injections of CCK_B receptor antagonists produced differential effects in LSF and HSF on amphetamine-induced sucrose intake (37). The finding that CCK_B receptor antagonist treatment potentiated amphetamine-induced activity in animals with low, but not high, DAergic tone (18) suggests that LSF have elevated levels of endogenous CCK_B activation. Indeed, CCK_B receptor activation inhibits DA release (23,42). Together, these results suggest that under certain circumstances LSF may possess elevated endogenous levels of CCK_B receptor activity, in relation to HSF. In light of the considerable data implicating CCK_B receptor activation in anxiety-like responses in humans (2,8) and laboratory animals (11,17,30,47), these results are consistent with the hypothesis that LSF demonstrate heightened anxiety-like behavior in the present study due to elevated levels of endogenous CCK. We are currently testing this hypothesis.

CONCLUSION

The present results suggest that individual differences in oral sucrose, but not chow, intake are predictive of behavioral reactivity in animal models of anxiety such as the EPM and ASR paradigms. Based upon indirect evidence, we have suggested several neurochemical systems that may contribute to these effects. However, the underlying mechanisms mediating individual differences in sucrose feeding and anxiety remain to be elucidated. These results may have implications for the design of useful preclinical screening tools to be utilized in the assessment of putative anxiolytic medications.

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