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Exploring Adaptations to Famine: Rats Selectively Bred for Differential Intake of Saccharin Differ on Deprivation-Induced Hyperactivity and Emotionality

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In many mammals, including humans and rats, acute starvation increases locomotor activity. This seemingly paradoxical and potentially lethal behavior pattern may reflect an evolved, multisystem response to sudden threats to metabolic homeostasis. The present study provides a novel test of this idea. Occidental High- (HiS) and Low- (LoS) Saccharin-Consuming rats differ on the taste phenotype and also on some affective measures, on which LoS rats score higher. Wheel running was measured in HiS and LoS rats with food available freely versus for 1 hr daily. As predicted, restricted feeding stimulated significantly more running among LoS rats. Two independent tests of emotionality (acoustic startle, stress-induced analgesia) also distinguished the lines. The confluence of taste, emotion, and reactivity to starvation conditions in species as distantly related as rats and humans points to integrated biobehavioral systems that warrant further exploration.

The venerable concepts of metabolic homeostasis and "set point" can be challenged in interesting ways. An example is the excessive exercise that often accompanies reduced food intake in humans and other animals (Epling & Pierce, 1996; Pierce & Epling, 1997; Vincent & Parð, 1976). For humans, this pattern is associated with the clinical diagnoses of anorexia and bulimia nervosa (American Psychiatric Association, *DSM IV*, 1994). Because activity increases in starvation conditions – when conserving energy seems more logical – deprivation-induced hyperactivity (DIH) is sometimes termed "paradoxical" or, in humans, "irrational" and "self-destructive." Its occurrence in intact, healthy rats, however, implicates phylogenetically old systems, perhaps constituting co-evolved adaptations to famine: Although relocating during a severe food shortage would consume resources and not guarantee survival, it may have, on balance, conferred a selective advantage over remaining in a depleted food patch (Pierce & Epling, 1996).

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Deprivation-induced hyperactivity, then, may be an integrated biobehavioral response to severe metabolic challenges. If rats and humans share mechanisms critical to this response, correlates of vulnerability to DIH in rats should correspond to markers of eating disorders in humans, such as family history of and comorbidity with emotional lability (Davis, Kennedy, Ralevski, & Dionne, 1995; Dess, 1991; Halmi *et al.*, 1991; Herpertz-Dhalmann, Wewetzer, Schulz, & Remschmidt, 1996).

Selective breeding is a powerful means of studying the genetic and functional relationships among behavioral processes. The Occidental High- and Low-Saccharin Consuming outbred rat lines (HiS, LoS) were developed to study individual differences in taste and their correlates (Dess & Minor, 1996). Since the second generation, the lines have differed in saccharin intake but have not differed consistently in body weight or daily chow or water intake. Tests in early generations also suggested that relative to HiS rats, LoS rats are more emotionally reactive as assayed by open-field behavior and stress-induced anorexia. Convergent evidence of linkage between taste and emotionality similarly has been obtained in rat strains selectively bred on active avoidance (Brush *et al*., 1988) and ethanol intake phenotypes (Overstreet *et al.*, 1993, 1997; also see Dess, Badia-Elder, Thiele, Kiefer, & Blizard, 1998; Gosnell & Krahn, 1992; Grahame, Li, & Lumeng, 1999), as well as in humans (DeMet et al., 1989; Dess & Edelheit, 1998). This convergence provides a strong basis for predicting that LoS rats will be more vulnerable than HiS rats to DIH. The present paper reports a test of this prediction, as well as results of two independent tests of emotionality.

Experiment 1

Method

Subjects. The rats were experimentally naïve females from four litters in each line from Generations 19 and 20 (LoS, $n = 9$; HiS, $n = 9$), averaging 91 postnatal days of age ($\forall$ 4 days, SEM) at the start of the experiment. Rats lived individually in a running wheel apparatus on a 12:12 light:dark cycle (lights off at 19:00) and had access to tap water throughout the study. Purina 5001 chow was freely available until the experiment began.

Apparatus. Nine running wheels with activity counters and an attached housing compartment (Lafayette Instruments 86041, Lafayette IN) were used, each by one HiS and one LoS rat in two successive mixed-line replications. Because DIH may vary as a function of diet (Beneke & Vander Tuig, 1996; Chiel & Wurtman, 1981), its magnitude was assessed on three equicaloric diets (1.65 calories per g); ingredients included 5001 chow meal, corn starch, glucose, mineral oil, corn oil, water, and cellulose (recipes at www.oxy.edu/departments/psych/DESS/INGRED~1.htm). The control diet was 58.3% carbohydrate, 28.4% protein, and 12.3% fat, by weight; respective values for the Low Protein/High Carbohydrate diet were 82.7%, 5.0%, and 12.3%, and for the Low Protein/High Fat diet were 58.3%, 5.0%, and 36.7%. Food was provided fresh daily in a glass jar with a metal holder, with foil in the bedding tray underneath the jar to collect spillage.

Procedure. On the first day in the running wheel apparatus, chow mash (1 g Purina 5001 chow meal to 1 g water) was freely available. For the next four days, the control diet was freely

available. Each rat then received a DIH test with one of the three diets. A test consisted of two phases: a *free-feeding* phase (three days), and a *restricted feeding* phase (two days) during which the diet was available for one hour daily (17:00–18:00 h). A *recovery* phase (two days then began, during which the control diet was freely available. Each rat was tested twice more, with the other two diets. In all, three rats in each line received the diets in one of three orders comprising a balanced Latin square design.

Data collection and maintenance began at approximately 16:00 h daily. Food intake and wheel revolutions were recorded daily. Because extraction from the apparatus was stressful for many rats, we opted not to weigh them daily, but rather only every 2-3 days to ensure maintenance of at least 85% initial body weight. No rats showed signs of malaise, dropped below 85% preexperimental body weight, or were withdrawn from the study.

Experimental and maintenance procedures were in accordance with institutional policies for the humane care and use of laboratory animals. For all statistical tests, "significance" was defined as $p<.05$.

Results

During the five-day baseline period, food intake (chow mash or control diet), activity, and body weight did not differ significantly between lines (see Table 1 for these measures and saccharin intake phenotype scores).

Figure 1 depicts activity during free feeding and restricted feeding on each of the three test diets. Relative to HiS rats, LoS rats ran more during free feeding and, more importantly, increased their activity more when access to food was restricted. These line differences were replicated on all three diets. The absolute amount of activity among LoS rats was remarkable; on the second day of restricted feeding on the Low Protein/High Fat diet, they averaged more than seven miles (wheel circumference x revolutions). As shown in Figure 1, recovery upon refeeding was complete on the first recovery day in both lines.

Two Line x Diet x Day mixed design analysis of variance (ANOVAs) were run on the activity data. The first ANOVA, on data from free-feeding days, yielded main effects of line, $F(1, 16) = 6.78$, and diet, $F(2, 32) = 5.95$ (by Newman-Keuls pairwise comparisons, Control < Low Pro/High Carbo < Low Pro/High Fat). In the second ANOVA, activity on each day of the restricted-feeding days was transformed to a difference from activity on the immediately prior free-feeding day, and these change scores were analyzed. The main effects of line and day were significant, $F(1, 16) = 22.84$ and 25.26, respectively.

In view of nonhomogeneity of error variance on some days, nonparametric tests were conducted to determine whether apparent line differences were inflated by parametric analysis. A Mann-Whitney *U* test was used to compare activity of the two lines on each of the nine free-feeding days (three on each of three diets) and to compare their change in activity from prerestriction levels on each of the six restricted-feeding days. The lines differed on none of the free-feeding days (all Us ≥ 22; ps$\geq$.10). They did, however, differ significantly on all but one of the six restricted-feeding days (Us, respectively, of 18 and 17 on Control diet, 6 for Day 2 on

Low Pro/Hi Carbo diet, and 15 and 7 on Low Pro/Hi Fat diet); the exception was the first day on the Low Protein/High Carbohydrate diet (U = 22, p=. 10). Whereas the line difference in free-feeding activity is tenuous, the differential increase in activity when access to food is restricted is robust.

Table 1
Characteristics of LoS and HiS rats in Experiments 1, 2a, and 2b (mean ±SEM)

	Experiment 1	Experiment 2a		Experiment 2b
Initial body weight		*Generation 10*	*Generation 19-20*	
LoS females	297.4 ±8.9	312.1 ±13.6	356.2 ±14.3	302.7 ±7.0
HiS females	310.4 ±19.5	326.2 ±10.6	307.0 ±13.4	304.0 ±21.0
LoS males	--	469.9 ±25.2	535.0 ±22.8	--
HiS males	--	480.1 ±6.2	493.8 ±17.5	--
Phenotype score				
LoS females	2.4 ±4.0	2.2 ±2.4	2.4 ±6.4	1.2 ±2.2
HiS females	34.0 ±4.3	51.0 ±2.5	45.3 ±5.9	38.6 ±6.7
LoS males	--	5.7 ±2.5	5.2 ±1.6	--
HiS males	--	28.6 ±3.5	35.2 ±5.8	--
Chow mash baseline				
Activity (revolutions/day)				
LoS females	530.1 ±128.8			
HiS females	684.4 ±290.3			
Food intake (g)				
LoS females	23.0 ±4.0			
HiS females	28.0 ±2.7			
Control diet baseline				
Activity (revolutions/day)				
LoS females	811.6 ±94.6			
HiS females	817.3 ±92.6			
Food intake (g)				
LoS females	33.2 ±2.2			
HiS females	27.3 ±2.6			

Note. The phenotype score is saccharin solution intake (ml) in a 24-hr two-bottle test, expressed relative to a pre-established daily water baseline and body weight (g): [(saccharin – water baseline)/body weight] x 100. A score of 0 indicates saccharin intake equal to normal daily water intake.

ANOVAs on food intake data yielded no line differences. Significant effects during free feeding included the main effect of diet, $F(2, 32) = 4.43$ (by Newman-Keuls pairwise comparisons, Control = Low Pro/High Fat < Low Pro/High Carbo), and day, $F(2, 32) = 10.75$ (Day 1 < Day 2 = Day 3). During restricted feeding, effects of diet, $F(2, 32) = 5.04$ (Control = Low Pro/High Fat < Low Pro/High Carbo,), and day, $F(1, 16) =$

9.27 (Day 1 < Day 2) on change scores (from the last free-feeding day) were significant.

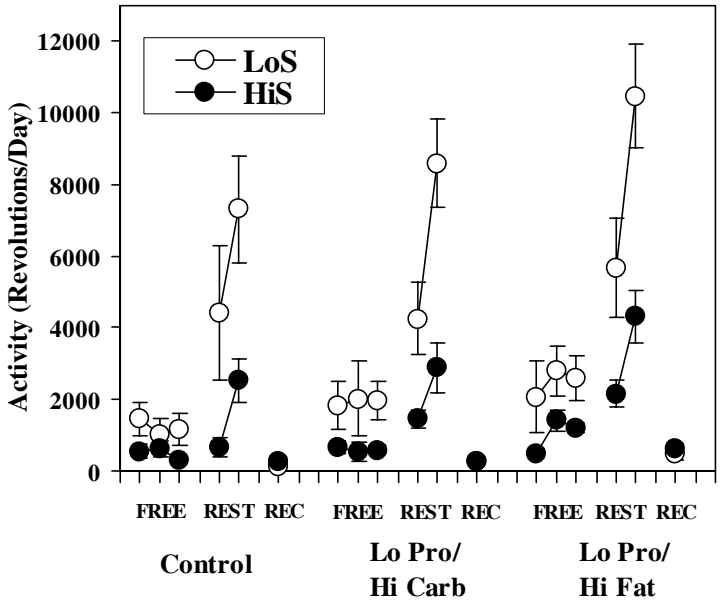

Figure 1. Experiment 1: Total daily revolutions in a running wheel (mean ±SEM) of HiS and LoS rats when one of three equicaloric diets was available freely (*Free*) or for one hour daily (*Rest*.) and for the first of two recovery days (*Rec*.).

Discussion

As predicted, LoS rats responded more vigorously to simulated famine conditions than did HiS rats. The present data hint at modulation of line difference by the type of diet available, but interactions of line with diet were not significant. Perhaps longer term exposure to protein-deficient diets would yield a more robust effect. Short- (Prasad & Prasad, 1996) or long-term (Dess, Choe, & Minor, 1998) maintenance on a high-fat diet modulates the impact of stress, so study of differential response to such diets also would be of interest. Further work is necessary to determine the extent to which expression of individual differences depends on dietary variables such as macro- and micronutrient composition, caloric density, novelty, palatability, and maintenance period.

There is little doubt that, were restricted feeding to continue, LoS rats would die sooner (Morrow *et al*., 1997). It does not follow, however, that LoS are less "fit" than are HiS rats or that their behavior is maladaptive in some absolute sense. Exaggerated DIH could be either lethal or life-saving in free-ranging rats, depending on the duration and severity of the food shortage and on whether increased activity led the animals to a food source. In this regard, DIH is indicative of *behavioral scaling*, "variation in

the magnitude or in the qualitative state of a behavior which is correlated with stages in the life cycle, population density, or certain parameters in the environment" (Wilson, 1975, p. 20, as cited in Goldsmith, 1994). Both LoS and HiS rats display DIH but to different degrees; this variability constitutes a substrate for ongoing selective pressure on this response to scarcity.

Experiment 2

Our working hypothesis is that differential DIH is one index of individual differences in the magnitude of an integrated biobehavioral response to environmental emergencies. The rapidity with which DIH recruits--within 24 hr of restricted food access--indicates that the response is not to life-threatening weight loss but rather to a sudden, threatening environmental change and its physiological sequelae. Our hypothesis implies that other measures of emotional reactivity also should distinguish the lines.

The first paper concerning the LoS and HiS rats included evidence of greater emotionality and stress reactivity in LoS rats in open-field and stress-induced anorexia tests (Dess & Minor, 1996). Here, we report two additional emotionality measures. The first (Experiment 2a) is acoustic startle. Startle is an evolutionarily old, brainstem-mediated reflex that is sensitive to descending, forebrain-mediated processes (Davis, 1997). Of particular interest here is the potentiation of startle amplitude by negative affect in rats and humans (Lang, 1995), a phenomenon commonly experienced by people as an exaggerated "jump" to noises during a scary movie. Both conditioned signals for aversive stimuli and ethologically relevant unconditioned anxiety – to bright illumination in rats, darkness in humans – increase startle amplitude (Grillon, Pellowski, Merikangas, & Davis, 1997; Walker & Davis, 1997). Thus, LoS rats' hypothetically greater reactivity to threats, such as transport to and testing in a novel startle apparatus, should elevate startle amplitude relative to HiS rats.

The second emotionality measure (Experiment 2b) is *stress-induced analgesia* (Kelly, 1986). In many species, prior exposure to any of a range of stressors inhibits withdrawal from painful stimuli. One functional analysis of this phenomenon is Bolles and Fanselow's (1980) perceptual-defensive-recuperative theory of fear and pain. On this view, environmental threats increase the salience of fear-relevant stimuli, such as predator cues and escape routes, and motivate defensive behavior. Pain-motivated recuperation would interfere with the urgent business of defense and thus is inhibited until the emergency has passed. (See Meagher et al., 2001, concerning the role of affect versus pain perception in "analgesia."). To the extent that LoS rats react more strongly to threats than do HiS rats, they should show more pronounced stress-induced analgesia--in the present

study, this would manifest as longer latencies to display the recuperative behavior of paw licking in a high-stress condition.

Method

Subjects. Experimentally naïve male and female rats from earlier (Generation 10; mean age 91 ± 4 postnatal days) and later (Generations 19-20; mean age 101 ± 3 postnatal days) generations, representing eight litters in each line, were used in two replications comprising Experiment 2a; all *n*s = 8, except for $n = 7$ for HiS males in the second replication due to the elimination of one ill rat. Experimentally naïve female rats from Generations 17-18 (mean age 88 ± 6 postnatal days), representing four litters in each line, were used in Experiment 2b (LoS, $n = 10$; HiS, $n = 10$). (See Table 1 for body weights and phenotype scores.) All rats were maintained in individual cages on a 12:12 light:dark cycle (lights off at 19:00 h) with Purina 5001 chow and water freely available.

Apparatus. Startle testing was conducted in a startle chamber with a piezoelectric sensor and digital display of platform force in arbitrary units (San Diego Instruments, San Diego CA); the startle stimulus was a 40-ms, 100-dB burst of white noise on a 65-dB masking noise background. Analgesia testing was conducted with two hotplates (Model 39D, IITC Life Science, Inc.) set at 48.5°C, one located in the vivarium and one in a room approximately 10 m away, to which the rats were not exposed prior to analgesia testing.

Procedure. In Experiment 2a, rats received 5-min handling experiences on two consecutive days, followed by a startle test consisting of 30 (first replication) or 18 (second replication) trials on a 10-s fixed-time schedule. In Experiment 2b, rats received 30-s handling experiences on two consecutive days, followed by two analgesia tests three days apart. For each analgesia test, the rat was placed in the center of the hotplate, where it remained until either of two observers saw it lift and lick a hind paw, or until 120 s elapsed, at which time it was picked up and returned to its homecage. One test took place in the familiar vivarium and the other took place after transport to the remote and novel location, with half of the rats tested first in each condition. Latency(s) to paw-lick was the dependent variable.

Results

Experiment 2a. Startle amplitude scores were parsed into 3-trial blocks, and each rat's median value of the three for each block was analyzed. This technique eliminates the occasional outlier, including ceiling values (for our apparatus, of 2000 in arbitrary units), yet yields group means and statistical significance virtually identical to analysis of three-trial block means. Group means are shown in Figure 2. In both replications, startle amplitude was significantly greater among LoS rats than among HiS rats and decreased over trial blocks. Informal comparison of earlier and later generations suggests that continuing selection on the saccharin phenotype has yielded somewhat lower within-group variability and divergence of the lines earlier in the startle testing session.

These data were analyzed in a Line x Sex x Trial block mixed design ANOVA for each replication. Because startle is measured by the amount of force delivered to a platform, individual differences in body weight could have an effect on the measured response magnitude. Thus, body weight (normalized within sex) was used as a covariate. In the first replication, body weight did not differ significantly between lines, but in the

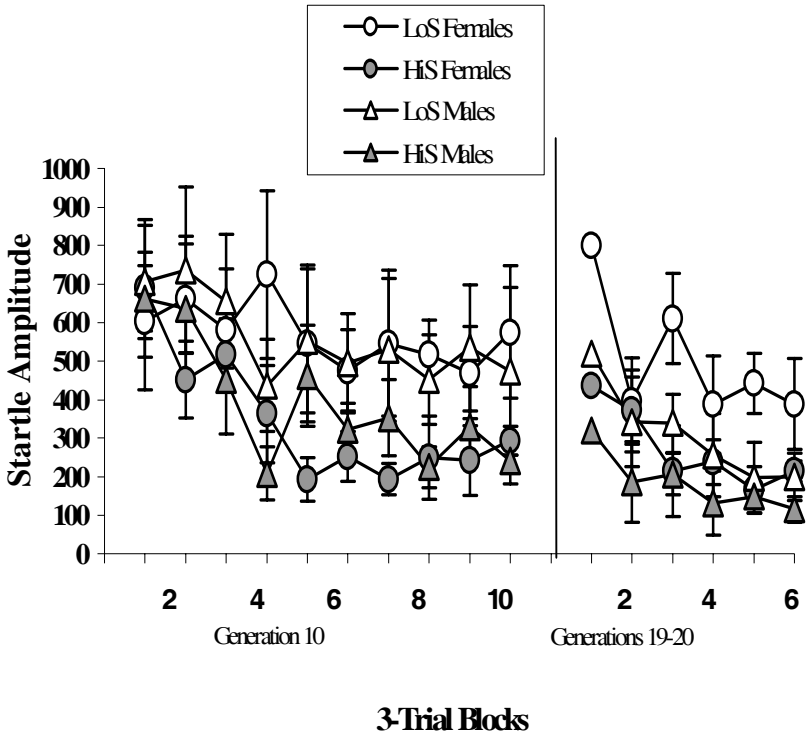

Figure 2. Experiment 2A: LoS and HiS rats' relative emotionality as assessed by acoustic startle amplitude (in arbitrary units, mean ±SEM) in Generation 10 (left panel) and in Generations 19-20 (right panel). Means are adjusted for body weight, normalized within sex.

second replication, LoS rats outweighed HiS rats, $F(1, 27) = 6.70$. Body weight did tend to covary positively with startle in both replications (i.e., rats heavier than their same-sex peers had higher startle scores). The covariation was significant in the first replication, $F(1, 27) = 7.83$, and nearly so in the second, $F(1, 26) = 3.68$ (p=.07). If body weight accounted for group differences in startle amplitude, then the line difference should have been significant in the second replication but not the first, and males should have had higher startle scores than females. Neither was the case.

In both replications, the main effect of line [$F(1, 27) = 4.27$ and $F(1, 26) = 7.21$, respectively] was significant, as was trial block [$F(9, 252) = 4.95$ and $F(5, 135) = 9.87$, respectively]. In addition, females tended to startle more than males; this difference was only significant in the second replication, $F(1, 26) = 5.88$.

Experiment 2B. Paw-lick latencies in the vivarium (Low Stress) and the remote location (High Stress) are shown in Figure 3. Longer latencies, indicating lower pain reactivity, occurred in the High Stress condition than in the Low Stress condition. More importantly, the difference between the Low Stress and High Stress conditions was larger among LoS rats than HiS

rats. A Line Stress condition mixed design ANOVA yielded a main effect of stress condition, $F(1, 18) = 27.32$, and a Line x Stress interaction, $F(1, 18) = 7.26$. A planned comparison using the error term from this ANOVA confirmed that the difference between test conditions was significantly larger in LoS than in HiS rats, $t(18) = 3.80$.

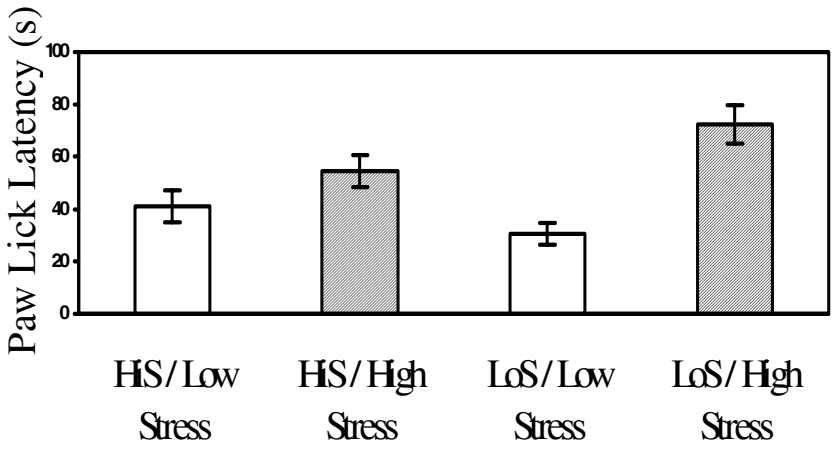

Figure 3. Experiment 2B: Stress-induced analgesia, depicted as the difference between paw-lick latencies (mean ±SEM) in Low Stress (open bars) versus High Stress (hatched bars) conditions (lower panel).

Discussion

Experiments 2a and 2b provide further evidence of a difference between LoS and HiS lines in reactivity to environmental stimulus change. As predicted, LoS rats display greater acoustic startle amplitude and stress-induced analgesia than do HiS rats. Elevated startle indicates facilitated stimulus processing, the mechanisms of which (e.g., attention, perceived magnitude, etc.) remain to be determined. Enhanced stress-induced analgesia has additional functional implications: In this paradigm, the LoS rats' greater reactivity to threat has consequences for behavioral organization. With pain-directed behavior more profoundly inhibited, fear and the defensive behaviors it motivates should dominate the response hierarchy. Direct, concurrent assessment of defensive and recuperative behaviors will be needed to determine the functionality of the line differences reported here.

General Discussion

As predicted, LoS rats are more vulnerable to deprivation-induced hyperactivity. This is the most compelling of several observations of a line difference in DIH in our lab. Selection on a saccharin intake phenotype has yielded lines that also differ on several behavioral measures commonly assumed to tap emotionality: Here, acoustic startle and stress-induced analgesia, and in prior work, open field defecation and stress-induced anorexia (Dess & Minor, 1996). By all of these measures, emotionality is greater among LoS rats than HiS rats.

Several important questions arise from these results. First, how stable is the clustering of these correlates? In the absence of replicate lines, we cannot say whether selecting again on the saccharin phenotype would yield the same pattern of results. We can, though, examine evidence from other projects involving similar measures. The most complete data come from studies of Roman Low- and High-Avoidance/Verh rats (RHA, RLA) and of two inbred mouse strains. The Roman lines were selectively bred on active two-way foot shock avoidance. RLA rats are often described as highly emotionally reactive. Relative to RHA rats, they defecate more in novel situations (Driscoll & Bättig, 1982), hyperstartle (Schwegler *et al*., 1997), and are more vulnerable to stress (Aguilar, Gil, Tobena, Escorihuela, & Fernandez-Tereul, 2000; Driscoll *et al*., 1998); they also consume less saccharin and ethanol (Razafimanalina, Mormede, & Velley, 1996). In short, RLA rats look very much like LoS rats when each is compared to its "high" phenotype counterpart. To our knowledge, DIH has not been assessed in the RLA/RHA, but we would predict that it would be exaggerated in RLA rats.

The same clustering occurs in two strains of inbred mice (C57BL/6J and BALB/c) that have been compared directly on tests of DIH and intake of saccharin and alcohol as well as open field behavior, acoustic startle, and stress vulnerability. Symons (1973) tested C57BL/6J and BALB/c mice in running wheels with and without food deprivation, and found that BALB/c mice were more reactive to food deprivation in terms of increased activity and reduced survival time. Since then, BALB/c mice have been characterized as more "emotional" or "anxious" than C57BL/6J mice (Kopp, Vogel, & Misslin, 1999; Lepicard *et al*., 2000), showing greater open field defecation (Makino, 1992), acoustic startle (Bullock, Slobe, Vasquez, & Collins, 1997; Paylor & Crawley, 1997), and stress vulnerability (Lu, Song, Ravindran, Merali, & Anisman, 1998; Shanks, Zalcman, Zacharko, & Anisman, 1991). Relative to C57BL/6J mice, BALB/c mice also drink less saccharin (Capeless & Whitney, 1995; Pelz, Whitney, & Smith, 1973) and ethanol (McClearn & Rodgers, 1961; Nachman, Larue, & Le Magnen, 1971).

Additional evidence of the correlation of saccharin with alcohol intake has been found in genetically heterogeneous rat samples (Gosnell & Krahn, 1992; Overstreet *et al*., 1993) and in mice selectively bred for differential alcohol preference (Grahame, Li, & Lumeng, 1999). An association between response to tastants and behavior in noningestive emotionality tests has also been reported in other high- and low-avoidance rat lines (SHA and SLA; Brush *et al*., 1988) and in a factor-analytic study of diverse rat lines (Overstreet *et al.*, 1997). Thus, selection on a range of phenotypes – or no selection at all – yields a recurrent association between taste and common measures of emotionality in rodents.

Based on available data, we cannot rule out alternative interpretations of LoS/HiS differences in individual tests in terms of sensory, motor, or associative processes – differences in auditory perception in acoustic startle or conditionability, for example. However, such interpretations are poor candidates as explanations for the pattern observed across sensory and behavioral systems for rat and mouse lines with very different origins.

As intriguing as this recurrent pattern is, it would be a mistake to gloss over potentially meaningful complications. For example, Maudsley Reactive (MR) rats were selected for high open field defecation and, relative to their Non-Reactive (MNRA) counterparts, consume less saccharin (Overstreet *et al*., 1993). However, ethanol intake by MR rats can be either higher (e.g. Satinder, 1982) or lower (Overstreet *et al*., 1993) than MNRA rats', and acoustic startle may not clearly distinguish the lines (Commissaris, Harrington, Baginski, & Altman, 1988). Animals bred for high alcohol preference consistently consume saccharin more avidly than controls but may have anxiety scores that are either unusually low (e.g., AA rats, Moeller *et al*., 1997) or high (P rats, Colombo *et al*., 1995, and McKinzie *et al*., 2000; sP rats, Stewart, Gatto, Lumeng, Li, & Murphy, 1993; see Viglinskaya *et al*., 1995). Finally, the degree of clustering among measures depends to some extent on selection phenotype as well as on the particular measure of emotionality (Overstreet, Rezvani, & Janowsky, 1992), stressor impact (e.g. Overmier, Murison, & Johnsen, 1997), or taste (preference versus volume consumed; Kampov-Polevoy *et al*., 1996).

Likewise, a broader review of the mouse literature – without the constraint of direct comparison of C57BL/6H to BALB/c – reveals a more complicated story. For instance, C3H/He mice resemble BALB mice and differ from C57BL/6J mice with respect to DIH (Symons, 1973), open field activity (Makino, 1992) and taste (Capeless & Whitney, 1995), and have been characterized as "emotional" (Kopp *et al*., 1999). We therefore would expect C3H/He to hyperstartle, but they startle *less* than C57BL/6J mice (Paylor & Crawley, 1997).

One of the challenges to resolving these puzzles lies in unraveling the construct of "emotionality," a project with a long and fruitful history.

Various techniques can distinguish emotionality from gross locomotor activity (e.g. Simmel & Eleftheriou, 1977) or learning ability (e.g. Brush *et al.*, 1985) and anxiety-like states from depression-like states (e.g. Commissaris, Verbanac, Markovska, & Altman, 1996). The issue of "basal" versus "reactive" aspects of emotionality has, however, proven a thornier theoretical (Ramos & Mormede, 1998) and methodological issue, in terms of establishing "true" baselines free of interventions that inadvertently shift them – carry-forward effects from repeated testing designs, handling, and so forth. In the present study, for instance, the longer paw lick latencies of LoS rats in the "High Stress" condition might have been interpreted as lower "baseline" pain sensitivity, had the "Low Stress" control condition been omitted and transport to a novel room been an invisible part of the testing protocol (e.g. Kampov-Polevoy *et al.*, 1996).

A related challenge arises from the host of conditions that modulate behavior in tasks commonly used to study emotional functioning – and that often vary between laboratories and studies. For example, in MR rats ethanol intake varies with the type of caging and how food is delivered (Adams, Sihabi, & Blizard, 1991), and their immobility in the forced-swim test depends on whether the water is fresh or soiled, more so than it does in MNRA rats (Abel, Altman, & Commissaris, 1992). In mice, the difference between C57BL/6J and BALB/c strains in open field behavior depends on rearing conditions (Chapillon, Mannechen, Belzung, & Caston, 1999) and apparatus illumination (Blizard & Bailey, 1979). An elegant, direct demonstration of "laboratory effects" is provided by Crabbe, Wahlsten, and Dudek (1999).

In light of the myriad variables that can work against finding consistency across studies of "emotionality," the observed degree of consistency speaks well of the construct's utility. However, the literature warns as much against facile appeal to the construct as against discarding it. The present work is more properly viewed as a contribution to the ongoing, iterative process of shaping the construct and its assessment – especially its functional and comparative dimensions – than as application of a widely agreed upon and well-understood concept.

Another important question concerns the mechanisms through which the clustering of measures occurs. Selective breeding immediately brings genes to mind. There are many reasons to suspect that genetic analyses will reveal differences between LoS and HiS rats. Heritability has been demonstrated for emotionality in SHA and SLA rats (Brush, Gendron, & Isaacson, 1999), which differ on the avoidance phenotype as well as open field behavior and stress-induced analgesia and finickiness (Brush *et al.*, 1988; Nagase, Randich, & Brush, 1985). Research with humans also has linked taste genetics to affective processes, including startle modulation, apprehensiveness, and depression (Carlson, Katsanis, Iacono, & McGue, 1997; DeMet *et al.*, 1989; Mascie-Taylor, McManus, MacLernon, &

Lanigan, 1983; Whittemore, 1986). Genetic analyses are well along with inbred mice: Quantitative trait loci analysis of emotionality implicates a pleiotropism involving mouse chromosomes 1, 2, and 15 (Flint *et al*., 1995); all of these have also been linked to saccharin and/or alcohol intake (Belknap *et al*., 1992; Vasdasz *et al*., 2000; Vasdasz, Saito, Gyetvai, Mikics, & Vasdasz, 2000).

Genetic variation cannot, of course, explain the behavior of LoS and HiS rats. To paraphrase Lykken (1995, p. 85), without experience, the rats' genome would produce no more than a damp spot on the bedding material. Prenatal exposure to stress hormones or opiates (Pfister, Golus, & McGee, 1981; Gagin, Cohen, & Shavit, 1996) and postnatal maternal behavior or handling (Fernandez-Teruel, Escorihuela, Driscoll, Tobena, & Bättig, 1991; Lasselle, Bulman-Fleming, & Wahlsten, 1991; Steimer, Escorihuela, Fernandez-Teruel, & Driscoll, 1998), may be critical to the expression of relevant genes. It is interesting to note that neonatal handling of RLA and RHA rats dramatically reduces the RLA rats' emotionality and diminishes the differences between lines (reviewed by Driscoll *et al*., 1998). While these effects can be viewed as alleviation of a "genetic deficit" (Escorihuela, Tobena, Driscoll, & Fernandez-Teruel, 1995), they also can be viewed in terms of the more general principle of the experience-dependency of gene expression. Even if genes distinguish LoS and HiS rats, observation of behavioral differences in adulthood may well hinge on prenatal and postnatal experience.

However strongly research implicates genetics in individual differences in emotionality, nonheritable mechanisms surely also contribute to variance in emotionality in natural populations. For example, the Borna virus has been linked to heightened emotionality in rats (Pletnikov *et al*., 1999) and to affective disorders in humans (Ferszt *et al*., 1999). If emotionality is indeed an emergent property of functionally integrated brain systems, proximal influence by environmental conditions is precisely what one would expect.

The third and last question concerns the centrality of energy regulation to the evolution of the biobehavioral substrates of emotionality. The idea of a relationship between emotion and energy is not new, dating back at least to Engle and Schmale's "conservation-withdrawal" in depression (Engle & Schmale, 1967). Still, the "primacy of energy regulation" is the most speculative assertion in our conceptual framework. Many selective pressures have been exerted on vigilance, defensiveness, and hedonic evaluation, and the relevant processes surely co-evolved. Consistent with this assumption, the literature reviewed above shows that selection on noningestive phenotypes ranging from open field defecation to active avoidance has yielded considerable convergence on emotionality measures. Yet the constancy of pressure on meeting metabolic needs -- particularly provisioning of glucose to the brain -- relative to other demands

suggests that energy regulation merits special consideration as an organizing concept.

A comprehensive examination of the primacy of energy regulation in emotional functioning is beyond the scope of this paper. Here, a précis of three cornerstone literatures outlines the argument. The first concerns the pervasive effects of severe feeding regimens in humans (e.g. Franklin, Schiele, Brozek, & Keys, 1948; Smith, Williamson, Bray, & Ryan, 1999). Particularly interesting in the present context is the occurrence of anorexia with or without excessive exercise. In commenting on variation within this clinical population, Caroline Davis and colleagues (1999) recently suggested, "over-exercisers may have had greater affective instability premorbidly" (p. 152).

The second perspective is behavioral ecology, in particular molar analyses of how animals organize their behavior to meet critical needs. Bronikowski and Altmann (1996) studied behavior patterns in wild-foraging and food-supplemented baboon troops and, among other things, assessed whether food availability was a more important limiting factor for resting or social behavior. Time freed up by reduced foraging demands was allocated disproportionately to resting rather than socializing, indicating the high premium placed on energy conservation even in highly social species. Laboratory-based foraging models, such as meal-patterning (Dess & VanderWeele, 1994) and operant regulation (Dess, 1997; Pierce & Epling, 1997), are sensitive to stress and can be useful tools in this approach.

The third perspective is experimental psychobiology. Some relevant work documents stress-alleviating effects of sugar in models including learned helplessness (Minor & Saade, 1997), ambient cold (Ahlers, Shurtleff, Schrot, Thomas, Paul-Emile, 1993), adrenalectomy (Bell *et al.*, 2000), and distress in rat and human infants (Blass & Shide, 1994; Smith & Blass, 1996). Direct assessment of metabolic processes has revealed a relationship between individual differences in energy expenditure and emotionality in mice (Friedman, Garland, & Dohm, 1992) and rats (Boakes, Boot, Clarke, & Carver, 2000); the latter included evidence of taste correlates as well. In our lab, LoS and HiS rats respond differently to rapid-onset pharmacological metabolic challenges (fast-acting insulin, 2-deoxyglucose; unpublished data).

Energy regulation is a concept approachable at many levels of analysis and, even focusing just on ingestion, through several entry points. Why attend particularly to taste, as a means of understanding the orchestration of energy regulation systems through emotionality? Taste operates, quite literally, at the interface between the external world and the internal milieu (Scott, 1987). As such, taste is a "sentinel," positioned to have roles in environmental monitoring, physiological regulation, and behavioral organization. Substances being tasted are poised to enter the body; the behavioral imperative is clear. More than a just-so story, the high

stakes of taste evaluation are consistent with a large literature on the emergence early in vertebrate evolution of hedonic responses to bitter and sweet tastes and the elaboration of these responses into complex neural, behavioral, and social systems (Dess, 1991; Rozin, 1996). Taste, then, is a good candidate as a marker for the animal's reactivity to threats to metabolic homeostasis.

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