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Temporal Organization of Eating in Low- and High-Saccharin-Consuming Rats

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When, where, and how much animals eat are influenced by food scarcity and risk of predation. The present study concerned the mediation of risk-related feeding patterns by emotion. Occidental Low-saccharin-consuming (LoS) and High-saccharin-consuming (HiS) rats, which differ in both ingestion and emotionality, were studied in three steady-state paradigms: an "open economy" procedure (discrete session cyclic-ratio operant schedule) and two "closed economy" procedures (meal patterning, free feeding with running wheel access). Cyclic-ratio performance showed better defense of stable food intake against variable cost among LoS rats. In closed economies, LoS rats consumed a larger number of smaller meals and showed a more pronounced circadian rhythm in meal initiation and running than HiS rats. Taste finickiness appears to serve as a marker for heightened cross-modal risk reactivity, the expressions of which include tighter behavioral regulation of eating in conditions of scarcity and exaggerated nocturnality.

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For many species, eating poses a high-stakes dilemma. On one hand, animals must eat or they die. On the other hand, eating can be risky because food can be toxic and because procuring or consuming food exposes the animal to environmental dangers. This dilemma is particularly acute for opportunistic omnivores who are both predator and prey, such as rats and humans (Agrawal, 2003). For them, food selection and the organization of eating in time and space are shaped by myriad mutually constraining internal and external variables.

Figure 1 schematically represents such an animal in an ecological context (from Dess, 1991). The figure depicts two interfaces between internal processes comprising energy balance and external variables comprising the dietary niche. "Eating and absorption" mark, respectively, the mouth and gut, each of which is a semi-permeable barrier between the animal and its environment. "Foraging" marks the interface between the niche and the animal's molar behavior within it. Processes operating at these interfaces influence, and are influenced by, variables on both sides of the interface. Rather than emphasizing the distinctiveness of inner and outer spaces (e.g. *gut defense* versus *skin defense*, Garcia, 1989), this model integrates them. Evidence concerning many of the relationships is presented in Dess (1991), as is the argument that negative affect can be usefully conceptualized in terms of shifts in energy regulation. For instance, one adaptive response to a fresh whiff of lurking predator is to hide and meet metabolic needs by utilizing calories stored as glycogen or fat rather than venturing out to forage. From this

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perspective, short-term weight loss after exposure to a stressor reflects an orderly shift in energy regulation rather than dysregulation (Dess, 1997; Dess, Choe, & Minor, 1998).

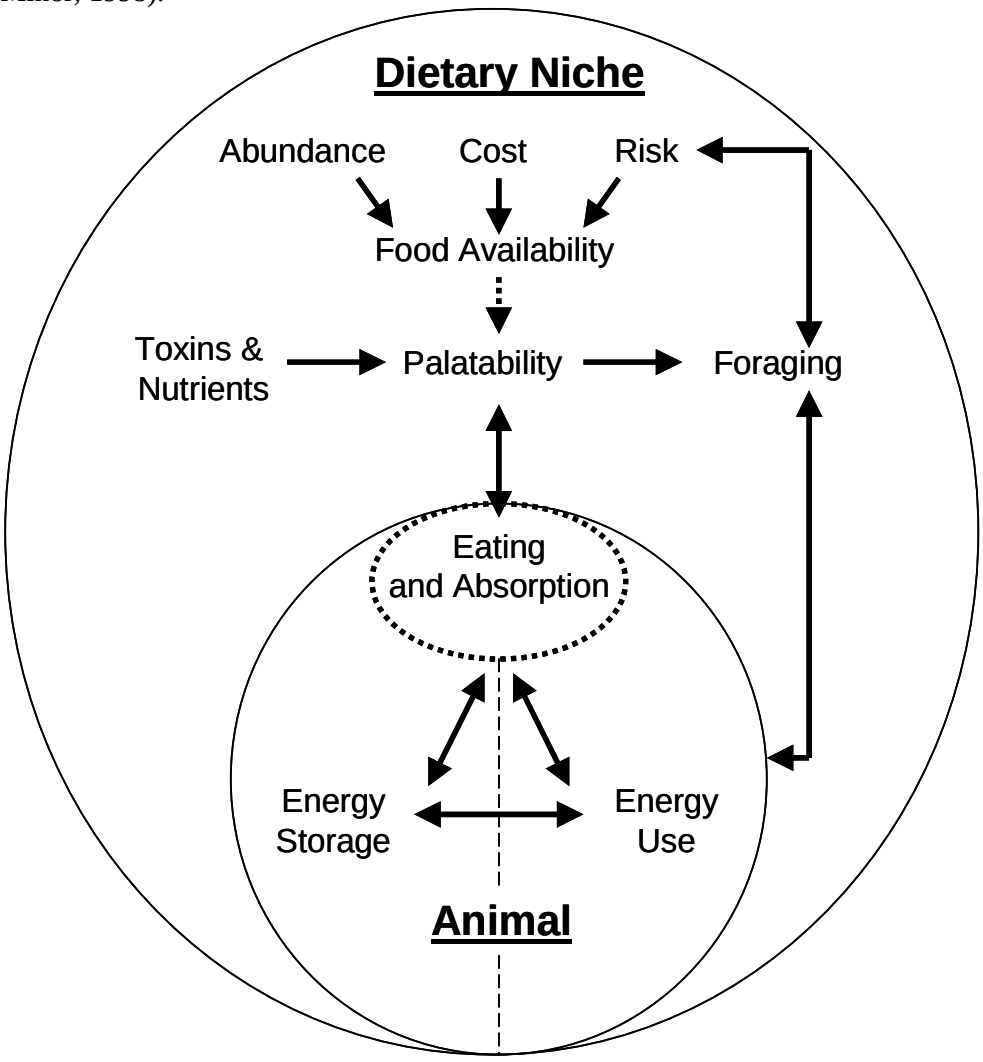

Figure 1. Schematic representation of an animal in its dietary niche, depicting energy balance, ecological constraints on eating, and some interrelationships. Originally published in Dess (1991, with permission).

Our strategy for examining relationships depicted in Figure 1 centers on rats selectively bred for relatively low versus high saccharin consumption. The phenotypic trait used for selection is intake of 0.1% saccharin solution in a 24-hour two-bottle test as change from a water-only baseline, expressed relative to body weight (Δ%). As expected (Nachman, 1959), our line difference in saccharin intake emerged by Generation 3 (Dess & Minor, 1996) and stabilized quickly. In samples from Generations 3 through 30 in two laboratories, phenotypes average about 6Δ%

for LoS rats and 32Δ% for HiS rats (Carroll, Morgan, Anker, Perry, & Dess, 2008). LoS rats also consume less starch, salt, and sugar solution than do HiS rats; they also reject sucrose solution adulterated with quinine, but not with citric acid, at lower adulterant concentrations than do HiS rats (Dess, 2000). Body weight and baseline food and water intake do not consistently distinguish the lines.

The line differences go beyond gustation *per se*. Relative to HiS rats, LoS rats display more aversive taste reactivity to saccharin only after some experience with it (Thiele, Badia Elder, Kiefer, & Dess, 1997), are less prone to intravenous cocaine self-administration (Carroll, Morgan, Lynch, Campbell, & Dess, 2002), and eat less in response to rapid-onset hypoglycemia (VanderWeele, Dess, & Castonguay, 2002). Phenotypic correlates also include behaviors bearing no obvious relationship to appetitive motivation. Relative to HiS rats, LoS rats score higher on several measures of emotional reactivity including defecation in a novel open field (Dess & Minor, 1996), acoustic startle amplitude (Dess et al., 2000), ethanol withdrawal (Dess, O'Neill, & Chapman, 2005), and stress-induced hypoalgesia (Dess et al., 2000).

Line differences observed to date demonstrate a link between the saccharin phenotype and affective processes that are not unique to taste. What sort of linkage might it be? Possibilities include:

- genetic linkage, i.e. multiple genes in close chromosomal proximity are expressed as the selection phenotype and as its correlates;
- pleiotropism, i.e. one gene has several seemingly unrelated phenotypic expressions; and
- functional linkage, i.e. two or more phenotypic correlates play related roles in a *behavioral system* (or systems) comprised of spatiotemporally coordinated sensory, affective, and action-generating processes, such as eating and defense.

The present study focuses on functional linkage. Functionally connecting the saccharin selection phenotype to startle, defecation, withdrawal, and hypoalgesia presents a challenge: The stimuli, contexts and behaviors involved apparently have little in common, differing in sensory modality and locus (external, interoceptive), time scale (milliseconds to hours), and type of motor response (reflexive, consummatory, smooth versus striated muscle). However, the stimuli and situations do all have an aversive component, and the responses are all defensive. Thus, the diverse stimuli and responses could be inputs to or outputs from a *risk reactivity* mechanism sensitive to qualitatively different kinds of risk – risk associated with toxins, metabolic imbalance, dominant conspecifics, and predators. This pattern of phenotypic covariation in LoS and HiS rats may derive from differential risk reactivity, with LoS rats generally reacting as if risks are greater.

Risk reactivity as we conceive of it has counterparts in the human literature, such as *neuroticism*, *negative emotionality*, *trait pleasure*, and *negative affectivity* (Eysenck, 1979; Patrick, Curtin, & Tellegen, 2002; Russell & Mehrabian, 1977; Watson & Clark, 1984). The closest parallel may be with negative affectivity (NA), the disposition to experience aversive emotional states. Individuals high on NA show heightened, persistent reactivity to stressors; thus,

they experience more negative affect than do low NA individuals even under steady state conditions due to the lingering effects of past upsets.

Global affective constructs gave some ground over the last 20 years to more specific emotional modules (e.g. fear versus disgust, Lawrence, Murphy, & Calder, 2004). However, global constructs – e.g. *undifferentiated negative affect* and *core affect* – are again proving valuable in the study of temperament, emotion, and stress vulnerability (Clark, 2005; Nemanick & Munz, 1997; Reich & Zautra, 2002; Russell & Barrett, 1999). In models that integrate an affective valence factor (positive/negative) with specific emotion circuits, the former is more basic, generic, and evolutionarily prior. Generalizing across species with respect to emotion is tricky (Davidson, 2002). Given that it can be valid, risk reactivity is the sort of construct likely to apply across species who either are closely related or have confronted similar ecological problems, and comparative evidence supports this view (Gosling, 2001). We prefer the term risk reactivity to similar terms because *risk* is referential and ecologically grounded.

A domain in which risk reactivity clearly should be expressed is foraging. To the extent that LoS and HiS rats respond differently to external or internal signals for risk, they should forage differently. Pathways to and from "Foraging" in Figure 1 represent functional relationships that should distinguish the two lines. Two experiments to date bear on that prediction. In an early one (Dess & Minor 1996), LoS rats showed greater suppression of homecage food intake by a stressor than did HiS rats, an effect consistent with a regulatory shift toward utilization of stored nutrients. Later, we reported in this journal (Dess et al., 2000) that deprivation-induced hyperactivity (DIH) is greater among LoS rats. When fed one hour per day for two days, LoS rats run more than twice as much in a wheel as HiS rats. DIH arguably is an experimental foraging paradigm (Epling & Pierce, 1996): Severely limited access to food models famine, and the excessive activity it generates models migration in search of a richer food supply (Fessler, 2002; Guisinger, 2003). In terms of Figure 1, depletion of energy stores and increased energy utilization stimulate greater activation of general search behavior (Timberlake, 1984) in LoS rats. In both of those experiments, however, inferences about foraging are necessarily weak because eating was not measured with any precision. The purpose of the present study was to look more directly at eating regulation in LoS and HiS rats with food-rewarded operant procedures.

Food-rewarded operant procedures may be grouped into two general categories. In discrete session (or *open economy*) procedures, rats earn some of a daily food ratio in relatively short (<1 hr) daily sessions. In meal patterning (or *closed economy*) procedures, rats live and earn all of their food in the operant chamber. As noted by Staddon (1979), many of the quantitative relationships between procurement and food intake are the same in discrete and 24-hr sessions. Similarities should be expected given that both procedures require animals to regulate food intake as its cost varies. And, after all, session length and proportion of daily food earned in it are continuous experimental variables; they hardly could be behaviorally discontinuous.

From a behavioral systems perspective, though, the two types of procedure as usually implemented differ in important ways (Collier & Johnson, 1997;

Timberlake & Silva, 1995). For present purposes, the critical difference is overall food availability. In a typical discrete session procedure, rats are chronically food deprived. This experimental practice is ecologically valid: Wild cousins of laboratory animals do encounter and adapt to food scarcity (Holeckova & Chytil, 1963; Poling, Mickel, & Alling, 1990). However, eating by very hungry animals in a short discrete operant session arguably constitutes one meal, with the experimenter controlling when the meal starts and, by selecting conditions to avoid satiation, when it ends (Collier & Johnson, 1997). This type of procedure therefore can reveal little about how rats organize their eating into meal-eating bouts on a daily basis. (See Houston & McNamara, 1989, for a defense of open economies as foraging models.)

In a typical meal-patterning procedure, on the other hand, rats can earn all the food they want and maintain body weight except when adverse procurement schedules are used. They regulate meal initiation and termination and allocate time to other activities over the dark/light cycle, within constraints imposed by the experimenter. As a result, closed economies usually do not generate "the increase in response rate, ingestion rate, or general activity that is associated with increasing intermeal intervals in deprived or depleted animals" (Collier & Johnson, 1997, p. 168). A typical closed economy procedure has its limits. When standard operant chambers are used, alternative activities are few, and some components of the behavioral system (general search, stalking, food handling) are either not engaged or not measured. Compared to a typical discrete-session procedure, however, the organization of eating in time can be expressed more fully.

The studies of eating regulation described here employed both types of operant procedure. In Experiment 1, a powerful discrete session operant schedule was used – the cyclic ratio schedule. Meal patterning (Experiment 2) was examined in 23.5-hr sessions of continuous reinforcement. Results from the Experiment 2 led us to revisit activity and eating in running wheels as a foraging paradigm (Experiment 3). Differences between LoS and HiS rats in steady-state performance in these paradigms were assessed to further explore some of the hypothetical relationships depicted in Figure 1.

Experiment 1

The cyclic ratio schedule of reinforcement provides a means of distinguishing the roles in eating of energy balance and the incentive value of the reinforcer (Ettinger & Staddon, 1983; Staddon, 1979). In this schedule, several fixed ratio (FR) schedules occur in ascending and descending orders in strict alternation. An ascending and descending series comprise a cycle, and several cycles comprise a session. When average response rate on each schedule is plotted against the corresponding eating rate (pellets earned per minute on that schedule), the parameters of the best-fit function correspond to different aspects of meal eating (see Figure 2, from Dess, 1997). The slope indexes the degree to which eating is defended against variation in the work requirement, or *behavioral regulation*. The *x*-intercept – the point corresponding to an instrumental response rate of 0 – is the hypothetical eating rate for free food, or the *preferred eating rate*.

The elevation of the function (*y*-intercept) indexes *reinforcer quality*, with a higher value indicating higher quality.

Several idealized patterns of cyclic ratio performance are shown in Figure 2. A hypothetical rat generating a vertical best-fit function earns pellets at the same rate whatever the schedule of reinforcement, i.e. perfectly regulates eating rate. Shallower functions indicate more variation in eating rate, with maximum variation occurring when the response rate is constant.

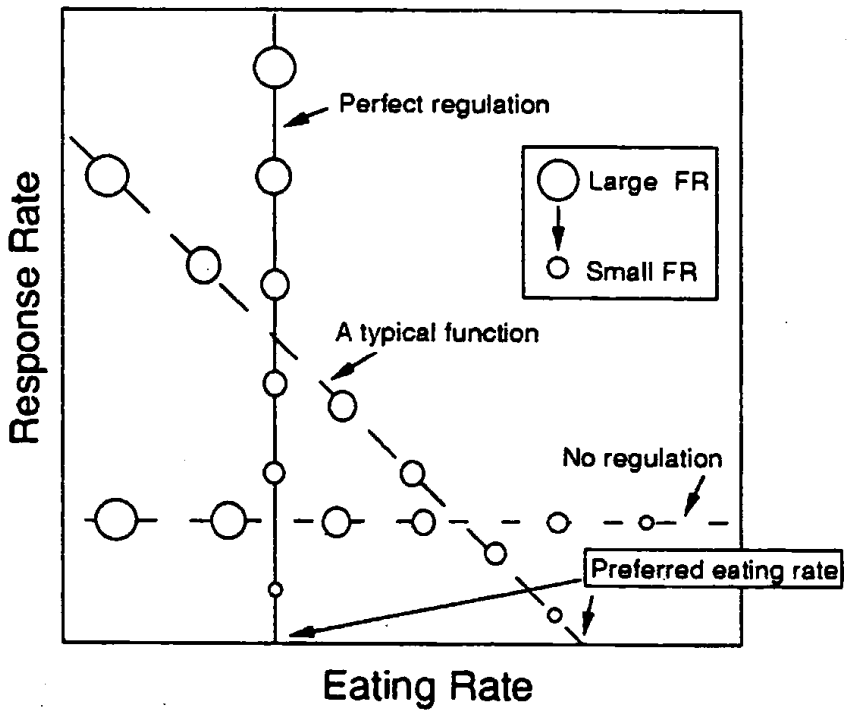

Figure 2. Idealized best-fit functions for cyclic ratio performance when response rate (bar presses/min) on fixed ratio schedules is plotted against eating rate (pellets/min). *Perfect behavioral regulation* refers to a constant eating rate (vertical function). *Preferred eating rate* refers to the hypothetical rate of consumption of free pellets (response rate equals 0). Originally published in Dess (1997, with permission).

Exposure to a long series of unpredictable, uncontrollable tailshocks reduces food intake in the homecage (Dess, Minor, & Brewer, 1989). We used the cyclic ratio schedule to assess the effect of that stressor on specific eating parameters (Dess, 1997). Consistent with reduced intake of free food in the homecage, preferred feeding rate (*x*-intercept) decreased from baseline; schedule control (*r*) was the same as during training, and behavioral regulation *improved* (steeper slope). In the aftermath of an encounter with a stressor, then, rats were not "dysregulated": They regulated pellet consumption better than before stress, albeit around a lower preferred rate.

Steady state cyclic ratio performance of LoS and HiS rats was examined in Experiment 1. LoS rats are more reactive to metabolic challenges including

hypoglycemia (VanderWeele et al., 2002) and restricted access to food (Dess et al., 2000). Thus, the chronic food deprivation required for stable performance on this schedule should constitute a greater stressor for LoS rats than for HiS rats. In the cyclic ratio paradigm, LoS rats' greater risk reactivity should be expressed as tighter behavioral regulation of eating (steeper slope) and a lower preferred eating rate (lower *x*-intercept) relative to HiS rats.

Method

Animals. The rats were 48 experimentally naïve adult female and male LoS and HiS rats from, respectively, six and seven litters of Generation 22 (*n*s = 12) (see Carroll et al., 2008, for selective breeding information). Initial body weights differed between females and males, $F(1, 38) = 255.33$, but not between lines (see Table 1). They were maintained at 85% of their pre-experimental weight with earned pellets and supplemental feeding of Purina 5001 rodent chow. They were housed individually on a 12:12 hr dark/light cycle, with light onset at 7:00 a.m. Care and use of the rats in this and the following experiments complied with institutional policies.

Apparatus. Sessions occurred in six computer-controlled standard operant chambers equipped with a lever and pellet dispenser. Each chamber was housed in a sound-attenuating box illuminated by a 7-w houselight. A ventilation fan provided some masking noise. The reinforcer was a nutritionally complete 45 mg pellet (#0021, Bioserv Inc., Frenchtown NJ).

Table 1
Initial Body Weight and Parameters of Best-Fit Lines for Cyclic-Ratio Performance Among Female and Male Rats in the LoS and HiS Lines (Mean ± SEM).

	LoS Females (*n* = 11)	LoS Males (*n* = 11)	HiS Females (*n* = 9)	HiS Males (*n* = 11)
Initial body weight (g)	278 ± 12	475 ± 10	281 ± 9	488 ± 16
Slope (Δ resp/pellet)**	-3.1 ± 0.5	-2.5 ± 0.6	-1.0 ± 0.3	-1.4 ± 0.3
x intercept (pellets/min)*	45 ± 9	66 ± 21	120 ± 60	146 ± 30
y intercept (resp/min)	102 ± 7	110 ± 10	85 ± 11	116 ± 11
r (schedule control)	0.76 ± 0.05	0.71 ± 0.06	0.63 ± 0.06	0.64 ± 0.06

* LoS ≠ HiS, $p < .05$
** LoS ≠ HiS, $p < .01$

Procedure. Each rat received one operant session per day between 1:00 and 4:00 p.m.. Supplemental feeding occurred 1 hr later. Rats received shaping followed by several sessions which progressed from FR1 to FR10 before cyclic ratio training began. Initial components of the cyclic ratio schedule were FR2, 4, 8, 16, 32, and 64. After a week on this schedule, four rats showed ratio strain at FR64 (two HiS males, two LoS males) and were shifted to a schedule comprised of FR1, 2, 4, 8, 16, and 32, which all completed. (Barring strain on high ratios, cyclic ratio performance parameters should be insensitive to the ratio values comprising the schedule.) After an additional week of training, six rats failed to meet a modest criterion for schedule control ($r \geq .30$; three HiS females and one rat in each of the other three groups) and were eliminated from the study. Final group size was $n = 9$ for HiS females and $n = 11$ for the other groups.

Rats earned 72 pellets (3.24 g of food) in each session. All 42 rats who met the schedule control criterion completed the last three training sessions quickly (less than 30 min) and consumed all of the pellets earned.

Statistical analyses. Mean response rate on each of the six FR schedules for each rat was

averaged over the last three training sessions. Dividing the mean response rate (bar presses/min) on each schedule by the schedule's value yielded the corresponding eating rate (pellets/min). Linear regression was performed on each rat's data (x = eating rates, y = response rates) to obtain four best-fit function parameters: slope (eating rate stability), x-intercept (preferred eating rate), y-intercept (reinforcer quality), and r (schedule control). Each parameter was subjected to a two-way analysis of variance (ANOVA) with line (LoS, HiS) and sex (female, male) as variables. Test statistics significant at $\alpha = .05$ are reported.

Results

Means and standard errors for each of the four meal parameters are shown by line and sex in Table 1. Best-fit functions were steeper and had lower x-intercepts for LoS rats than for HiS rats, Fs(1, 38) = 11.79 and 5.72, respectively. Thus, LoS rats' performance more closely approximates an idealized, vertical function depicting an eating rate that is constant regardless of work requirement. LoS rats' preferred eating rate, however, is lower than HiS rats'. No sex differences or line x sex interactions were significant. The line differences in slope and x-intercept are depicted graphically in Figure 3.

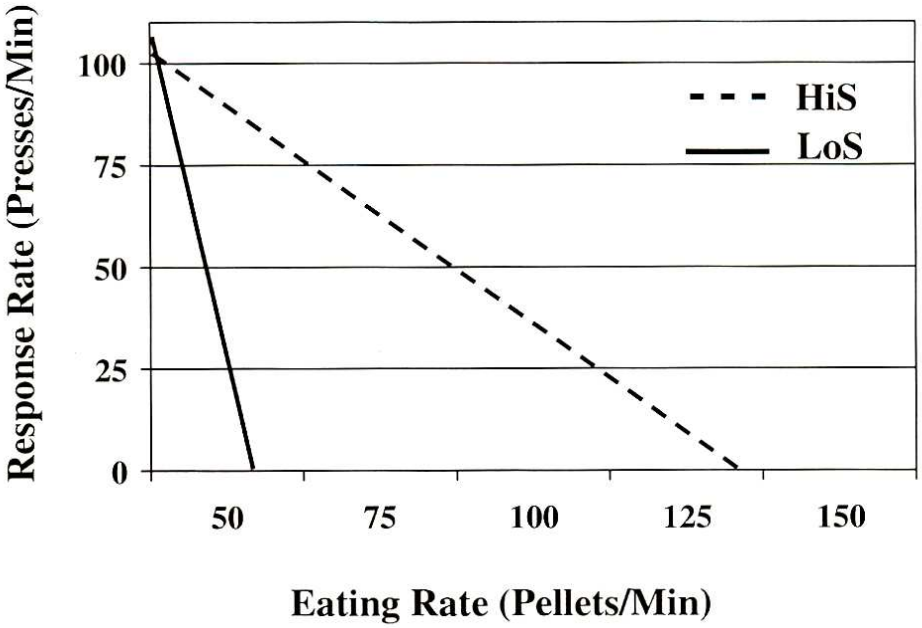

Figure 3. Data-based best-fit functions for the cyclic ratio performance of LoS (n = 22) and HiS (n = 20) rats. Average slope and x- and y-intercepts were used to plot the function for each line.

Skew, kurtosis, and nonhomogeneity of variance were present for x-intercepts. Though ANOVA is robust against these characteristics, x-intercepts were reanalyzed nonparametrically. A Mann-Whitney test comparing confirmed the lower preferred eating rate among LoS rats, U(20, 22) = 115.00.

Discussion

LoS rats more strongly defended eating rate across work requirements and had a lower preferred eating rate than did HiS rats. Thus, as predicted, chronically food deprived LoS rats behaved in the cyclic ratio paradigm as if they were responding to a greater stressor than HiS rats (Dess, 1997). In the previous study, tailshocks did not affect *y*-intercept, indicating no effect on reinforcer quality; similarly, in Experiment 1, LoS and HiS rats had comparable *y*-intercepts. Also, in the previous study, the slope of the best-fit function was only steeper than baseline after 100 tailshocks; neither restraint nor 20 tailshocks produced that effect. Thus, the present results suggest that LoS rats' heightened risk reactivity makes chronic deprivation functionally comparable to a major, rather than a mild or moderate, stressor.

LoS and HiS rats responded at equally high rates on the leanest schedule components, with LoS rats showing graded depression of response rates on richer schedule components. In addition, schedule control was equally high among LoS and HiS rats. LoS rats' instrumental response to a metabolic shortfall, then, is not to press the bar faster overall (to earn food faster) or slower overall (to conserve effort) or to behave erratically. Nor are they simply less hungry than HiS rats, as less severe food deprivation makes the best-fit function shallower (Staddon, 1979). Rather, compared to HiS rats, LoS rats more precisely titrate their effort to the work requirement to maintain a more stable, but lower, eating rate.

If discrete session procedures model single meals (Collier & Johnson, 1998), then it follows from the present results that the pace of eating within a meal should be lower among very hungry LoS rats than HiS rats when food is free, as would be the case if foraging led from a depleted patch to a rich one. This prediction is counterintuitive in the sense that one might expect rats who are more reactive to metabolic emergency to eat faster, not slower. It is, however, reminiscent of prior observations that LoS rats eat less than do HiS rats in response to hypoglycemia produced by fast-acting insulin or 2-deoxy-D-glucose (VanderWeele et al., 2002) and respond to food deprivation with a staggering *increase* in energy expenditure by running (Dess et al., 2000). Also, in the delay-discounting procedure, hungry LoS rats are more willing than HiS rats to tolerate a delay to earn a larger food reward (Perry, Nelson, Anderson, Morgan, & Carroll, 2007); the lines did not differ when cocaine was the reward, implicating energy regulation rather than generic incentive value in the effect. A more definitive answer to the question of whether very hungry foraging LoS rats who encounter free food actually will eat slower than HiS rats awaits further study.

In Experiment 1, females and males did not differ on any cyclic ratio performance parameter. More importantly, line differences in the parameters were statistically the same in females and in males. The line difference also has been essentially the same in females and in males in other studies with both sexes: Differences between LoS and HiS rats in open-field emergence (Dess & Minor, 1996), acoustic startle (Dess et al., 2000), and intake of flavored solutions and ethanol (Dess et al., 1998; Dess, 2000) were not sex specific. While the magnitude of the line difference sometimes differed between sexes, the direction of the

difference and its sensitivity to parametric manipulation were comparable in females and in males. Similarly, in the one study we have published on the taste/emotionality relationship in women and men, no sex differences in that relationship were observed (Dess & Edelheit, 1998). Thus, our studies to date of the relationship of saccharin phenotypes to somatic function provide no *a priori* reason to expect line differences to be unique to females or unique to males.

Experiment 2

The closed economy meal patterning paradigm has been used to study steady state organization, and reorganization, of eating (Clifton, 1999). In this paradigm, rats live in operant chambers and earn all of their food instrumentally. The distribution of meals in time as well as characteristics of individual meals, including meal size, duration, and pace of eating, are measured. When initiating a meal is made energetically costly with a high meal procurement response requirement, meal frequency decreases and meal size increases (Collier & Johnson, 1998). Another kind of cost to meal initiation is exposure to risk of predation (Lima & Dill, 1990), which has been modeled experimentally with intermittent, unpredictable electric shocks. Like high instrumental procurement cost, exposure to shocks in either another apparatus (Dess & VanderWeele, 1994) or the same apparatus (Fanselow, Lester, & Helmstetter, 1988; Helmstetter & Fanselow, 1993) reduces meal frequency and increases meal size and/or eating rate in a closed economy. In the latter two studies, total food decreased at the highest threat levels. Interestingly, the rats did not lose weight, suggesting that adaptation to an adverse foraging environment included increased energy efficiency.

If rats cope with a risky world by eating fewer meals, LoS rats might be expected to eat fewer, larger meals than HiS rats. Confidence about that outcome was compromised by the features of the closed economy necessary to getting a good look at steady state meal patterning. Put simply, the simulated foraging niche we created in Experiment 2 was not very risky. Food was cheap, unlimited, high quality, and controllable, and by the time steady state data were collected, the situation was familiar and predictable. Perturbations were minimal, more so than in regular vivarium life: Rats lived in sound-attenuating chambers without interruption except for a brief daily maintenance routine that did not include handling. Shock has never been administered to rats in the operant chambers, so stress odors would have been minimal.

This relatively safe world did have night and day. Rats are nocturnal, a lifestyle which reduces risk of predation. Endogenous and light-entrained processes mediate various aspects of nocturnality, including more frequent meal initiation in the dark (Strubbe & Woods, 2004). Light avoidance does not account entirely for reduced meal initiation. However, rats do prefer to forage in darker rather than lighter areas (Arcis & Desor, 2002; Whishaw, Dringenbeg, & Comery, 1992). More generally, risk reactivity is greater in the light than in the dark. In rats, darkness onset reduces several measures of emotionality (Nasello, Machado, Bastos, & Felicio, 1998), and vigilance and acoustic startle are greater in the light than the dark (Bertoglio & Carobrez, 2002; de Jongh, Groenink, van der Gugten, &

Olivier, 2003; Godsil & Fanselow, 2004; Whishaw, Dringenbeg, & Comery, 1992). Light enhancement of startle is not due to sensory stimulation *per se* because among humans, who are diurnal, acoustic startle is greater in the dark (Grillon, Pellowski, Merikangas, & Davis, 1997). Moreover, light enhancement and light/dark area choice in rats are attenuated by anxiolytic drugs (Chaouloff, Durand, & Mormede, 1997; Walker & Davis, 2002), implicating anxiety and not general arousal (Frankland & Ralph, 1995) in the effects. The organization of rats' behavior over the circadian cycle is best understood from an ethological perspective, as derived from an affect-modulated system for managing risk associated with time of day.

Because the one unambiguous risk in our meal-patterning protocol was simulated daytime, one prediction follows from the hypothesis that risk reactivity is higher among LoS rats: Relative to HiS rats, LoS rats should show a more exaggerated circadian rhythm in meal patterning. Our hypothesis is not helpful in guessing about the particular aspects of meal eating in which exaggeration should be most apparent. It is helpful to note that the biggest difference between dark and light feeding in rats is in meal frequency. Meal initiation is controlled by satiety signals (Strubbe & Woods, 2004; Zanutto & Staddon, 2007), and reduced satiety appears to be a proximate mechanism for more frequent meal initiation in the dark (Kraly, Cushin, & Smith, 1980). Therefore, LoS rats might be expected to show a larger difference between dark and light in meal frequency and in satiety than HiS rats.

If meal frequency does differ between the lines, meal size also should differ. Homecage food intake does not consistently differ between LoS and HiS rats, and the protocol in Experiment 2 was designed to model unconstrained eating as much as possible given a minimal operant requirement. Thus, if meal frequency differs between lines either overall or in the dark, compensatory differences in meal size should be observed. That is, if LoS rats eat more often, the meals should be smaller, such that total consumption does not differ between lines.

Method

Animals. The rats were 36 experimentally naïve adult male LoS and HiS rats (*n*s = 18) from, respectively, 11 and 15 litters of Generations 29 and 30. LoS rats were slightly heavier on average than HiS rats initially and when weighed before the saccharin phenotype test a few days post-experimentally, but neither body weight nor weight gain differed significantly between lines (see Table 2). Rats lived in operant chambers on a 12:12 light:dark cycle (lights on at 7:00 a.m.) with access to tap water throughout the study. Rat chow was freely available until the experiment began, after which rats ate pellets earned in the chambers.

Apparatus. The same operant apparatus and pellets as in Experiment 1 were used.

Procedure. Rats were preexposed to the 45-mg pellets in their homecages on the two days preceding placement in the operant chambers. Rats then were weighed and placed in the operant chambers where they could earn food pellets on a continuous reinforcement schedule (1 pellet per lever press). They remained in the chambers until training was complete. Any rat who did not learn the task the first night was given a supplemental chow feeding and another night to learn the task, which all did.

Daily at approximately 4:30 p.m., pellets and water were replenished, dropping pans were changed as needed, data were collected, and the program was restarted; the maintenance routine took approximately 30 minutes, so rats were free to earn meals for 23.5 hr daily. Meal initiation was defined as at least 10 pellets earned within 10 min, and meal termination was defined as 10 minutes

without a response (Dess & VanderWeele, 1994; Kraly et al., 1980). Military time at each meal initiation, intervals between the end of one meal and initiation of the next meal, meal duration, and number of pellets earned within the meal were recorded. Training continued until meal eating stabilized, defined as the number of meals varying by no more than two meals in three successive 23.5 hr periods. Stabilization occurred in about a week in both lines.

Statistical analyses. Meal parameters were averaged over the last three days of training. Parameters analyzed included number of meals and intermeal interval (minutes), meal size (pellets/meal), meal duration (minutes), within meal pace (pellets/min), and total pellets earned. Additional derived measures were analyzed. The first was *satiety ratio*, an index of how long a meal is delayed per pellet consumed in the preceding meal (intermeal interval/meal size; Kraly et al., 1980); a smaller value indicates more transient satiety.

Second, a measure of circadian rhythm was calculated for each meal parameter. To obtain a *dark ratio*, the average value for meals initiated in the dark phase was calculated and divided by the average for 23.5 hr periods. This transformation was used instead of direct comparison of dark phase to light phase values because the latter often would be based on few meals and thus would be unstable. Presence of a circadian rhythm is indicated by a dark ratio different from 0.5 for number of meals and total pellets earned and different from 1.0 for other parameters.

A series of three statistical analyses was performed. First, LoS and HiS groups were compared on the daily average for each meal parameter using independent *t*-tests. The other two analyses concerned circadian rhythm. To determine which of the parameters were, in an absolute sense, robustly sensitive to simulated daylight, the overall dark ratio for each meal parameter was assessed with a one-sample *t*-test (grand mean dark ratio collapsed across lines versus 0.5 or 1.0 as appropriate). Finally, LoS and HiS groups were compared on the dark ratio for each meal parameter using independent *t*-tests. All *t*s significant at $\alpha = .05$ are reported.

Table 2

*Body Weight and Meal Parameters for LoS and HiS Rats (*n*s = 18, Mean ± SEM. Parameters are Shown as 23.5 hr Average (First Line) and Circadian Dark/Light Shift (Second Line).*

	LoS	HiS
Initial body weight (g)	443 ± 8	428 ± 6
Post-experimental body weight (g)	483 ± 7	460 ± 7
Number of meals *	11.9 ± 0.5	9.6 ± 0.7
Dark ratio	0.83 ± 0.02	0.84 ± 0.02
Meal size (pellets/meal) *	52.6 ± 2.4	61.8 ± 3.5
Dark ratio	1.06 ± 0.02	1.07 ± 0.04
Intermeal interval (min)	86.7 ± 3.9	98.7 ± 8.2
Dark ratio **	0.78 ± 0.02	0.97 ± 0.06
Satiety ratio (IMI/Meal size)	1.67 ± 0.07	1.62 ± 0.12
Dark ratio*	0.74 ± 0.03	0.92 ± 0.06
Meal duration (minutes)	6.2 ± 0.6	6.7 ± 0.4
Dark ratio	1.11 ± 0.04	1.09 ± 0.06
Within meal pace (pellets/min)	9.2 ± 0.6	9.5 ± 0.5
Dark ratio	0.98 ± 0.04	1.00 ± 0.03
Total pellets earned	605.3 ± 16.0	559.2 ± 18.9
Dark ratio	0.80 ± 0.02	0.78 ± 0.03

* LoS ≠ HiS, $p < .05$
** LoS ≠ HiS, $p < .01$

Results

Daily meal parameter values

Means and standard errors for each meal parameter in an average 23.5 hr period are shown in Table 2. Compared to HiS rats, LoS rats ate more meals, independent $t(34) = 2.54$, and the meals were smaller, independent $t(34) = 2.15$. No other meal parameters differed between lines.

Parameters showing circadian rhythm

Dark ratios for each meal parameter also are shown in Table 2. Overall, a circadian rhythm occurred for every meal parameter except pace of eating within a meal. Number of meals, meal duration, meal size, and total pellets earned were higher in the dark phase, one-sample $ts(35) = 23.84$, 2.90, 2.76, and 16.85, respectively. Intermeal interval and satiety ratio were smaller in the dark phase, one-sample $ts(35) = 3.46$ and 7.78, respectively.

Line differences in circadian rhythm

Circadian rhythm was exaggerated among LoS rats by two measures. Dark ratios were smaller for LoS rats than for HiS rats for intermeal interval and satiety ratio, independent $ts(34) = 2.83$ and 2.64, respectively. Among HiS rats, the dark ratio for those parameters was close to 1.0, indicating that the time between meals was nearly the same in the dark as in the light, in terms of both absolute length and length relative to meal size. LoS rats, on the other hand, initiated successive meals sooner in the dark than in the light, in both absolute and relative senses. The dark/light phase difference was comparable in the two groups for all other meal parameters.

Body weight considerations

Supplemental analyses were conducted to determine whether the nonsignificant body weight difference between lines could account for significant line differences in meal parameters. Correlations of initial and post-experimental body weight with each meal parameter were examined, and meal parameters that distinguished the lines were reexamined with initial or post-experimental body weight as a covariate. Neither body weight measurement correlated with any meal parameter, and line differences in overall number of meals and meal size and dark ratios for intermeal interval and satiety ratio all remained significant when either body weight measurement was used as a covariate. Body weight does not explain the observed line differences in meal patterning.

Discussion

On average, LoS and HiS rats weigh about the same amount and eat about the same amount of food daily. Given the opportunity, however, they go about

provisioning themselves differently. LoS rats eat more frequently and show a stronger nocturnal pattern than do HiS rats. Specifically, LoS rats initiate meals in faster succession in the dark. Smaller meals do not explain this line difference because the satiety ratio takes meal size into account. LoS rats' relatively shorter intermeal intervals in the dark imply reduced generation of or sensitivity to satiety signals (Kraly et al., 1980). Candidate brain sites include the hippocampus and nucleus accumbens, lesions of which result in more frequent, smaller meals (Clifton & Somerville, 1994; Clifton, Vickers, & Somerville, 1998); potential neurochemical mediators include bombesin, gastrin-releasing peptide, insulin, and neuropetide Y (Lynch, Hart, & Babcok, 1994; McGowan, Andrew, Kelly, & Grossman, 1990; Strubbe & Woods, 2004). Satiety ratio did not distinguish the lines overall (i.e. 23.5 hr averages), indicating that the mechanisms of the LoS rats' reduced satiety in the dark are synchronized to the circadian cycle. Hypothalamic nuclei such as the suprachiasmatic and paraventricular nuclei may modulate the central or peripheral mediators of the line difference in the temporal distribution of meals (Strubbe & Woods, 2004).

We are disinclined to link LoS rats' higher meal frequency over 23.5 hr periods directly to risk reactivity. The kind of risk to which it might be a reaction is unclear. Their exaggerated circadian rhythm, on the other hand, clearly follows from heightened risk reactivity. This interpretation also is consistent with higher meal frequency in the dark among RLA/Verh rats (Rossi, Driscoll, & Langhans, 1997). Selection on the basis of two apparently dissimilar phenotypes – low saccharin intake and low active avoidance – seems to have yielded rats who score higher on diverse measures of risk reactivity (see also Brush et al., 1988).

Over 23.5 hr periods, LoS rats' meals were smaller than HiS rats' meals. Circadian variation in meal size did not differ between lines. Taken together, these results suggest that the robust difference between lines is the temporal distribution of meals, and that meal size is secondary to meal frequency. That is, regulatory signals such as cholecystokinin or insulin likely reduce LoS rats' meal size to compensate for high meal frequency, such that body weight and total food intake do not differ between lines either in the homecage or in an operant closed economy.

Relatively higher meal frequency in the dark among LoS rats is consistent with results from Roman Low Avoidance (RLA/Verh) rats who, relative to their High Avoidance counterparts (RHA/Verh), are more anxious (Steimer & Driscoll, 2005). Compared to RHA/Verh rats, RLA/Verh rats eat more frequently and have lower satiety ratios (intermeal interval relative to meal size) in the dark phase. That two pairs of independently selected lines of rats distinguished on measures of anxiety differ in these ways strongly implicates anxiety in these aspects of eating regulation.

In contrast to meal frequency and size, within meal pace of eating did not distinguish LoS and HiS rats. Moreover, pace of eating showed no circadian variation. These results concur with Collier & Johnson's (1998) observation that ingestion rate is independent of intermeal interval in closed economies. The results also suggest that the LoS rats' lower preferred eating rate in Experiment 1 was indeed contingent on chronic deprivation.

Other variables also must influence within meal pace of eating. Whereas freely feeding RLA/Verh rats eat more slowly than their RHA/Verh counterparts (Steimer & Driscoll, 2005), LoS rats earn "cheap" food more slowly than HiS rats only when very hungry. Similarities between LoS and RLA/Verh rats probably only go so far, and procedural differences such as level of dietary fat and meal definitions might contribute to the discrepancy (Castonguay, Kaiser, & Stern, 1986). Even if so, puzzles remain. For instance, Whishaw, Dringenberg, & Comery (1992) reported that rats ate faster at night in the colony than during the day in the test apparatus but, within the apparatus, ate *slower* in relatively safe dark areas than in riskier light areas. They attributed the reversal to "time sharing" between surveillance and eating in uncovered areas of the apparatus. For present purposes, the important point is that compared to pace of eating, circadian variation in meal initiation more robustly distinguishes the LoS and HiS lines and their RLA/RHA counterparts.

Experiment 3

In Experiment 2, LoS showed an exaggerated circadian rhythm in meal initiation. But is nocturnality in general more pronounced among LoS rats? The answer to that question ought not be based on a single instrumental response. Concluding that the pattern of lever-pressing models foraging and reflects the overall activity or quiescence of the rats in dark and light phases requires convergent evidence from another paradigm. In Experiment 3, LoS and HiS rats lived in apparatuses equipped with a running wheel for six days, with food freely available. Wheel running and grams of food intake were measured separately for the daytime hours (9:00 a.m. – 5:00 p.m.) and for the dark and transitional hours (5:30 p.m. – 8:30 a.m.). The question was whether LoS rats would show a more pronounced circadian rhythm in running than HiS rats. In Experiment 2, rats earned more pellets in the dark than in the light, and the lines did not differ in this respect. Thus, no line difference in the circadian rhythm for food intake is predicted.

Method

Animals. Eighteen experimentally naïve adult female LoS and HiS rats from, respectively, four and three litters in Generation 9 were used (*n*s = 9).[1] Rats lived in running wheels on a 12:12 light:dark cycle (lights on at 7:00 a.m.) with continuous access to food and water.

Apparatus. Six stainless steel running wheels (101 cm circumference) with mechanical activity counters and an attached housing compartment (Lafayette Instruments 86041, Lafayette IN) were used. Purina 5001 rodent chow pellets or chow mash (1:1 chow:water) was provided fresh daily in a glass jar with a metal holder, with foil in the bedding tray underneath the jar to collect spillage. A water bottle was attached to the housing compartment.

Procedure. The rats were weighed and placed in a running wheel apparatus. For three days, pelleted chow was freely available and the wheels were locked to allow adaptation to the new environment. For the next six days, chow mash was freely available and the wheels were unlocked. Mash was used to avoid the wheel jamming that can occur with pelleted chow. Data collection occurred at 8:30 a.m. and 5:00 p.m. daily. Body weight was measured in the morning, and food intake and wheel revolutions were recorded at both times. Water bottles were refilled and bedding was changed as needed during the 5:00 p.m. data collection period.

Statistical analyses. Average chow intake during the adaptation period and initial and terminal body weights in the two lines were compared with independent *t*-tests. To account for the different lengths of the light and dark/transitional phases, wheel revolutions and mash intake in each phase were transformed to per-hour averages. Running and eating in the dark and light phases were analyzed in separate mixed design ANOVAs with line (LoS, HiS), phase (dark, light), and test day (Day 1-6) as variables. Test statistics significant at $\alpha = .05$ are reported.

Results

Chow intake during the adaptation period did not differ between lines (LoS *M* = 20 ± 1 g *SEM*, HiS *M* = 18 ± 2 g *SEM*). Body weight did not differ between the lines either initially (LoS *M* = 294 ± 11 g *SEM*, HiS M = 275 ± 10 g *SEM*) or on Day 6 (LoS *M* = 291 ± 10 g *SEM*, HiS M = 274 ± 8 g *SEM*).

Average wheel revolutions per hour in the dark and light phases is shown in Figure 4. Both groups ran more in the dark than in the light, but the dark/light difference was larger among LoS rats than HiS rats. This difference grew over the six day test period. Every main effect and interaction in a 2 x 2 x 2 x 6 ANOVA was significant, all *F*s > 4, *p*s < .01. Of chief interest here is the line x phase interaction, $F(1, 16) = 8.00$. A planned comparison of the dark/light difference averaged across test days in LoS and HiS rats was significant, $t(16) = 2.83$. In view of nonhomogeneity of variance, the average dark/light difference was subjected to a Mann-Whitney test, which confirmed the line difference, $U(9, 9) = 17.00$.

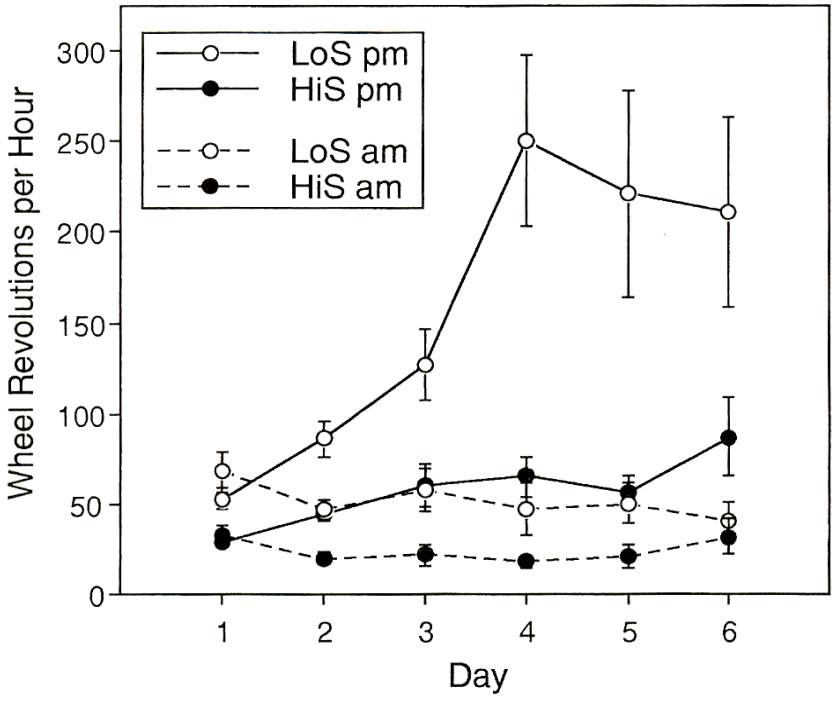

Figure 4. Running wheel activity (revolutions per hour) during the dark/transitional phase (pm) and the light phase (am) in LoS and HiS rats. Food was freely available.

Average hourly food intake (calories per kg of bodyweight) in the dark and light phases is shown in Figure 5. Eating increased over test days, and rats ate more in the dark phase than in the light phase. These effects were comparable in LoS and HiS rats. A 2 x 2 x 2 x 6 ANOVA yielded significant main effects of day, $F(5, 80) = 25.20$, and phase, $F(1, 16) = 11.26$. No other effects were significant.

Both lines maintained their body weights well over the testing period; average weight change was -3 ± 2 g for LoS rats and -2 ± 4 g for HiS rats. A 2 x 6 mixed design ANOVA on body weight (not shown) with line and day as variables yielded no significant effects. In addition, neither initial nor terminal body weight was correlated with food intake or running on any test day, and average light-versus-dark difference in activity remained significant when initial or terminal body weight was used as a covariate.

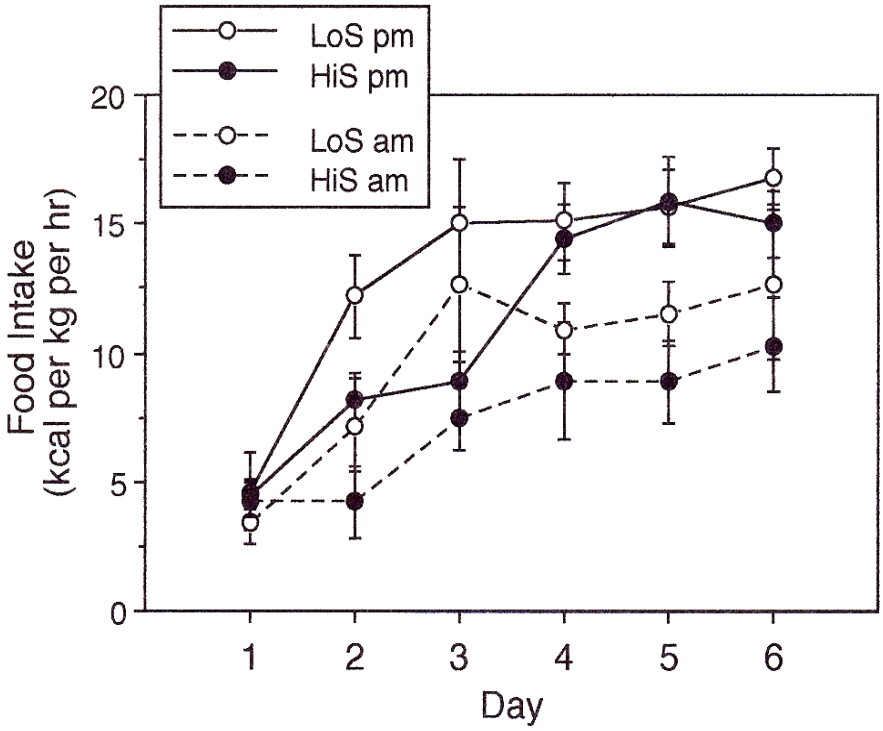

Figure 5. Food intake (calories per kg of bodyweight per hour) during the dark/transitional phase (pm) and the light phase (am) in LoS and HiS rats.

Discussion

Relative to HiS rats, LoS rats with access to a running wheel and an unlimited supply of free food show an exaggerated circadian pattern of locomotor activity. These results indicate that the greater shift in meal frequency between dark and light phases among LoS rats in Experiment 2 was not unique to meal initiation or bar-pressing. Rather, it is part of a more general line difference in organization of behavior over the circadian cycle.

One interpretation of the line difference in wheel running is that LoS rats are more active in general. This interpretation is contradicted by other findings. First, at the end of the test period, LoS rats were not more active than HiS rats during the light phase, while the difference in the dark persisted. Second, in Experiments 1 and 2, LoS rats did not have higher bar-pressing rates than HiS rats. Third, in an earlier study (Dess & Minor, 1996), LoS rats emerged more *slowly* into a novel open field than did HiS rats, consistent with great risk reactivity; moreover, when retested later in the open field, number of line crossings did not differ between lines. Thus, there is no convergent evidence of a line difference in general locomotor activity. To the contrary, in the present study, the line differences were contingent on reinforcement schedule, time since the last meal, and/or time of day. A "hyperactivity" interpretation fails to account for, much less predict, the sensitivity of line differences to circumstance.

Running and food intake increased early in the test period, stabilizing after a few days. These increases probably reflect adaptation to the novel environment, the running wheel, and the novel texture and lower caloric density of the chow mash. Interestingly, LoS rats maintained their body weight as well as did HiS rats despite running more. LoS rats ran approximately 2500 more revolutions – about 1.6 miles "farther" – than HiS rats on each of the last three days. LoS rats' slightly (nonsignificantly) higher caloric intake may have offset the weight loss that otherwise should accompany greater energy expenditure. However, other counterregulatory changes, such as reduced core body temperature, slower gastric emptying, or hypersomnia, also likely played a role.

Whereas male rats were used in Experiment 2, female rats were used in Experiment 3. Sex differences in wheel running might be expected on empirical (e.g. Epling & Pierce, 1996; Geary, 2001; Gentry & Wade, 1978) and theoretical (Houston, Stephens, Boyd, Harding, & McNamara, 2007) grounds. The relevant question here, however, is not whether females and males differ but whether the line difference in Experiment 3 occurs only in females. No cyclicity or untoward within-group variability is apparent. Also, as noted above, we have not yet observed a saccharin phenotype correlation unique to one sex. While circadian variation could be an exception, female rats are rats, and neither our reasoning about risk reactivity nor results to date support the idea that these results are unique to one sex.

General Discussion

The present results indicate that LoS rats show better behavioral regulation of eating when food is scarce and are more dedicatedly nocturnal then HiS rats. Better behavioral regulation and greater nocturnality may seem to connote that LoS rats are behaving more adaptively than HiS rats. Our protocols do engage biobehavioral systems that evolved under selective pressure, and our lines differ in how those systems function. However, characterizing either line as better adapted or more fit would be inappropriate. The heritability of the line differences is unknown. Moreover, whether better behavioral regulation of eating or an exaggerated circadian rhythm would confer an adaptive advantage outside of the

laboratory likely would depend of a range of ecological variables. Indeed, the phenotypic variation we are studying probably exists because the expression of the variants, and its consequences for fitness, are contingent on circumstance.

The present results support the idea that greater risk reactivity among LoS rats underlies a range of behavioral line differences. The common neural mediators of these diverse effects are not known. Aversive tastes activate the autonomic nervous system (Rousmans, Robin, Dittmar, & Vernet-Maury, 2000) and sucrose consumption ameliorates stress vulnerability among adrenalectomized rats (Dallman et al., 2003), with robust strain differences occurring in the latter effect (Pecoraro et al., 2006). Thus, pathways connecting taste to hypothalamic-pituitary-adrenal (HPA) mediated stress responses, and phenotypic variation in their functioning, do exist. LoS rats are hypercorticosteronemic (VanderWeele et al., 2002), so central and peripheral regulation of HPA activity may play a role in line differences in the organization of eating.

Implications of foraging theories (McNamara & Houston, 1985) for the relationship between risk reactivity and the organization of eating also warrant consideration. Optimality and momentary maximizing both have some empirical support as foraging principles (e.g. MacDonall, Goodell, & Juliano, 2006). To the extent that rats have the capacity to operate in either manner, perhaps the energetically conservative LoS rats have a greater tendency toward optimality whereas HiS rats, consistent with their greater impulsivity (Perry et al., 2007), would tend toward momentary maximizing.

The present results also may speak to greater risk sensitivity in LoS rats. In this context, the risk to which the term *risk sensitivity* refers is uncertain food reward, and sensitivity to it is typically assessed as choice between constant and variable reinforcement when pay-offs are equal. Risk aversion is defined as preference for the former and risk proneness as preference for the latter (Bateson, 2002; Kacelnik & Bateson, 1996). Given greater risk reactivity among LoS rats, we might expect LoS rats to be more risk averse than HiS rats. According to the energy budget rule, a shift from positive to negative energy balance should increase risk-prone foraging (Hastjarjo, Silberberg, & Hursh, 1990; Ito, Takatsuru, & Saeki, 2000; Kaminski, & Ator, 2001). How energy balance affects risk proneness in LoS and HiS rats is unclear, though. LoS rats should be more reactive to negative energy balance and thus show a greater shift toward risk proneness than HiS rats, but a general tendency to avoid food uncertainty would mitigate such a shift. Parametric manipulation of food variability and energy balance might reveal different “tipping points” between risk aversion and proneness in the two lines rather than just a general tendency toward one or the other.

A particularly appropriate approach to using LoS and HiS rats to understand the relationship between risk reactivity and foraging would combine food supply- and predator-related risk. The *cognitive-emotional forager* model (Coleman, Brown, Levine, & Mellgren, 2005) incorporates trade-offs between approaching food and avoiding predation as a function of energy balance. This quantitative model would allow assessment of the relative importance of food supply, danger of predation, and hunger in the foraging strategies of LoS and HiS rats. An important complementary concept is *predatory imminence*. Fanselow &

Lester (1988) distinguished stages in the predation sequence from the perspective of prey including, in order of increasing imminence, pre-encounter, post-encounter, and circa-strike stages. The stages are associated with qualitatively different anti-predation strategies. In predator-simulating procedures, we might expect LoS rats to modify their foraging and other behaviors in ways suggestive of a higher degree of predatory imminence. A variety of stressor manipulations followed establishment of the steady-state behaviors reported here, constituting pilot work on how increased predatory imminence would affect behavior in these paradigms and whether LoS and HiS rats are affected in different ways or to different degrees. More systematic examination of those questions clearly is warranted.

The present results encourage continued attention to dispositional variables in the attempt to account for eating in ecological context. Future work with LoS and HiS rats in experimental preparations incorporating manipulation of energy balance, food quality, explicit predator-associated cues, spatial dimensions of foraging, and richer behavioral topographies will further that effort.

[1] A preliminary report on total running averaged over the last two days appeared in a book chapter (Dess, 2001), but running on the other four days, food intake and body weight were not reported, and light and dark phase data were not disaggregated.

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