Combined Dieting and Stress Evoke Exaggerated Responses to Opioids in Binge-Eating Rats

Mary M. Boggiano, Paula C. Chandler, Jason B. Viana, Kimberly D. Oswald, Christine R. Maldonado, and Pamela K. Wauford
University of Alabama at Birmingham

The authors developed an animal model of binge eating where history of caloric restriction with footshock stress (R + S) causes rats to consume twice the normal amount of palatable food. The authors tested the hypothesis that binge eating is mediated by changes in opioid control of feeding by comparing rats’ anorectic and orexigenic responses to naloxone and butorphanol, respectively, and by testing the ability of butorphanol to elicit binge eating of chow when palatable food was absent. Mu/kappa opioid-receptor blockade and activation had exaggerated responses in the R + S rats with naloxone suppressing binge eating to control levels, and although butorphanol did not trigger chow binge eating, it enhanced binge eating of palatable food. These responses in sated normal-weight rats strengthen evidence that reward, over metabolic need, drives binge eating.

Keywords: hyperphagia, intermittent palatable food, naloxone, butorphanol, caloric restriction

We have developed an animal model of stress-induced binge eating that allows us to study the physiology of abnormal drive and intake of highly palatable (HP) foods (Geary, 2003; Hagan, Chandler, Wauford, Rybak, & Oswald, 2003; Hagan et al., 2002) in rats with a history of both cyclic caloric restriction and footshock (R + S). We have previously demonstrated that R + S rats consume unusually large quantities of HP food in a discrete period of time under sated conditions. The amount of intake is larger, as is their proportion of HP food to chow eaten, than occurs in hungry rats without similar histories of restriction and stress following several days of caloric restriction. These behaviors, as well as the predisposing factors (caloric restriction and stress), simulate clinical binge eating as occurs in bulimia nervosa, binge-eating disorder, and binge-purge-type anorexia nervosa (American Psychiatric Association, 1994; Freeman & Gil, 2004; Mitchell, Hutschenreiter, Eckert, & Pyle, 1985; Polivy & Herman, 1985; Stice, Presnell, & Spangler, 2002). We first predicted that restriction and stress might work synergistically to increase food intake on the basis of observations that caloric restriction is the strongest predictor of stress-induced overeating in the nonclinical human population (Greeno & Wing, 1994; Polivy & Herman, 1999). Our animal model of binge eating supports this synergistic effect because stress evokes binge eating only in rats with a history of cyclic caloric restriction (Geary, 2003; Hagan et al., 2002, 2003).

Little is known about the neurochemical changes that mediate binge eating. This is the first study aimed at elucidating the physiology of this animal model of binge eating and should point to critical physiological targets that are altered when restriction and stress are experienced in combination. We identified the central nervous system (CNS) opioid system as a possible mediator of this response on the basis of several factors. First, although R + S rats were provided a choice between regular chow and HP food (Oreo cookies), the rats’ binges were due entirely to an increase in HP food intake (Hagan et al., 2002, 2003). Second, and strikingly reminiscent of restricting binge eaters (Abraham & Beumont, 1982; Hetherington & Rolls, 1991), R + S rats did not binge if chow alone, and not HP food, was present after stress; however, if these rats were allowed to consume just a morsel of HP food following stress, they proceeded to binge on chow (Hagan et al., 2003). This binge-triggering effect of HP food, along with its preferential intake under sated conditions, represents intake for hedonic (vs. metabolic) purposes, feeding that involves regulation by CNS opioids (Levine & Billington, 2004). Third, intermittent intake of HP food, which is a critical component of this stress-induced animal model of binge eating, has been shown to increase mu-receptor binding in mesolimbic nuclei and to produce naloxone-precipitated symptoms of opioid withdrawal (Colantuoni et al., 2001; Kelley, Will, Steininger, Zhang, & Haber, 2003; Spangler et al., 2004). However, it is not known if opioidergic control of food intake is involved in binge eating that develops in response to intermittent access to HP feeding when coupled with cycles of restriction–refeeding and environmental stress. Intermittent consumption of HP food is common in individuals who binge eat, as is a history of caloric restriction and stress. Because we concurrently tested three control groups in this binge-eating protocol—a group of rats with a history of restriction but no stress (R + NS), a group with stress but no history

Mary M. Boggiano, Paula C. Chandler, Jason B. Viana, Kimberly D. Oswald, Christine R. Maldonado, and Pamela K. Wauford
Department of Psychology, Behavioral Neuroscience Division, University of Alabama at Birmingham.

Mary M. Boggiano has previously published as Mary M. Hagan.

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Correspondence concerning this article should be addressed to Mary M. Boggiano, Department of Psychology, 415 Campbell Hall, 1300 University Boulevard, University of Alabama at Birmingham, Birmingham, AL 35294-1170. E-mail: boggiano@uab.edu
of restriction (NR + S), and a group with neither a history of restriction nor stress (NR + NS)—we were able to infer the effects of a history of caloric restriction and environmental stress, both alone and in combination, on opioid regulation.

We conducted a pharmacological test of the hypothesis that changes in opioid function mediate binge eating by first measuring the feeding responses to opioid-receptor antagonist treatment in rats adapted to binge eat (R + S rats) and comparing their intake with that of the three control groups. We then compared feeding responses in these groups following opioid-receptor agonist treatment. Lastly, we tested the capacity of an opioid-receptor agonist to trigger binge eating when only chow, and not HP food, was available. Our results provide the first evidence to suggest that a history of cyclic caloric restriction and stress alter opioid regulation and that it is this change that is an important mediator of binge eating.

Method

Subjects

A total of 25 ninety-day-old female Sprague–Dawley rats were acclimated to individual bedded cages under a 12-hr light–dark cycle (lights off at 1100) with ad lib chow and water for 1 week prior to caloric-restriction cycling. The rats were then weight-matched into the four groups (n = 6–7 per group) described above (NR + NS, NR + S, R + NS, and R + S) and in previous studies (Hagan et al., 2002, 2003). The University of Alabama at Birmingham Institutional Animal Care and Use Committee approved all procedures used in this study (Approved Protocol No. 031107030).

Development of Binge Eating

Binge eating was produced in the R + S group by subjecting the rats to three restriction–refeeding cycles. Each cycle lasted 12 days. As outlined in Table 1 and in accordance with group assignment, the cycle started with ad lib or restricted chow intake, followed by refedding on ad lib chow and HP food (cookies), and ending with ad lib chow only. At the end of each cycle, rats in the stress groups (i.e., R + S, NR + S), and a group with neither a history of caloric restriction nor stress (NR + NS)—we were able to infer the effects of a history of caloric restriction and environmental stress, both alone and in combination, on opioid regulation.

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Diets and Drugs

The chow used was from Harlan Teklad Diets, Indianapolis, IN (3.3 kcal/g; 69.8%, 3.5%, 16.7%, and 10.0% of kilocalories from carbohydrate, fat, protein, and moisture, respectively). The HP food was Nabisco Oreo cookies from Kraft Foods, Chicago, IL (4.7 kcal/g; 57.0%, 43.0%, and trace kilocalories from carbohydrate, fat, and protein, respectively). Naloxone HCl, primarily a mu- but also a kappa- and weaker delta- and sigma-receptor antagonist (Sigma-Aldrich, St. Louis, MO), was injected intraperitoneally at a dose of 1 mg/kg. Butorphanol tartrate, primarily a kappa- and mu-agonist with some affinity for the delta-receptor agonist (Sigma-Aldrich, St. Louis, MO), was injected intraperitoneally at a dose of 8 mg/kg. This naloxone dose is one that suppresses food intake in rats, especially those maintained on HP diets (Hagan, Holguin, Cabello, Hanscom, & Moss, 1997; Kanarek, Mathes, Heisler, Lima, & Monfared, 1997; Rudski, Billington, & Levine, 1997; Shabir & Kirkham, 1999; Weldon, O’Hare, Cleary, Billington, & Levine, 1996; Yeomans & Clifton, 1997). The dose of butorphanol was previously determined by Mary M. Boggiano (formerly Mary M. Hagan) to elicit overeating in rats with similar histories of caloric restriction but not in controls (Hagan & Moss, 1991). In the present study, these doses of naloxone and butorphanol proved subthreshold for altering food intake in the control groups, facilitating measurement of the drugs’ anorectic and orexigenic responses in the R + S group.

Stress-Induced Feeding and Drug Tests

A stress-induced feeding test was conducted immediately following time in the footshock alley. This test consisted of returning rats to their home cages with ad lib chow and cookies. Food intake and spillage were measured after 2 hr and 4 hr (in the dark) and after 24 hr (which included some feeding in the light from 2300–1100). To establish the permanency of binge eating in R + S rats, rats in this study were cycled two additional times beyond the third cycle, after which R + S rats have been shown to initially engage in binge eating (Hagan et al., 2002, 2003). Representative results from one of these cycles are presented (Cycle 6). Drug tests were performed at the end of subsequent cycles. Immediately following time in the footshock alley, rats were returned to their home cages and allowed to feed on chow and cookies for 2 hr prior to drug injections. Multiple previous feeding tests following stress had confirmed that differences in food intake between groups never occurred until 2 hr after stress, so the rats were injected at the time when binge eating in the R + S group would be most pronounced (from Hours 2–6 after stress). First, naloxone and saline were administered in counterbalanced fashion (over Cycles 8 and 9 for all rats to receive both drug conditions). They were injected just after 2 hr of feeding following stress as described above. Second, a minimum of two more cycles was allowed before the butorphanol and saline tests, which were performed over the course of two more cycles (Cycles 12 and 13) following the same procedures used for the naloxone/saline experiment. Third, and also following a minimum of two drug-free cycles, 8 mg/kg butorphanol and saline were administered immediately after stress in counterbalanced fashion across two more cycles (Cycles 16 and 17) to test the ability of butorphanol to trigger binge eating of chow when only chow, and not HP food, was available. These procedures replicated those used in a previous study in which a taste of HP food was used to trigger binge eating.

Table 1

Schedule of Caloric Restriction–Refeeding and Stress Conditions for One Cycle That Produced Binge Eating in R + S Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Days 1–5</th>
<th>Days 6–7</th>
<th>Days 8–11</th>
<th>Day 12 a.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR + NS</td>
<td>ad lib chow</td>
<td>ad lib chow &amp; cookies</td>
<td>ad lib chow</td>
<td>no stress</td>
</tr>
<tr>
<td>NR + S</td>
<td>ad lib chow</td>
<td>ad lib chow &amp; cookies</td>
<td>ad lib chow</td>
<td>stress</td>
</tr>
<tr>
<td>R + NS</td>
<td>66% of controls’ chow</td>
<td>ad lib chow &amp; cookies</td>
<td>ad lib chow</td>
<td>no stress</td>
</tr>
<tr>
<td>R + S</td>
<td>66% of controls’ chow</td>
<td>ad-lib chow &amp; cookies</td>
<td>ad-lib chow</td>
<td>stress</td>
</tr>
</tbody>
</table>

Note. Intakes were recorded after 2 hr and 4 hr (on Day 12) and after 24 hr (on Day 13), immediately after which Day 1 of the next cycle commenced. NR + NS = no history of caloric restriction and no stress; NR + S = no history of caloric restriction and stress; R + NS = history of caloric restriction and no stress; R + S = history of caloric restriction and stress.
eating of chow (Hagan et al., 2003). Prior to all nondrug and drug tests, the
previous day’s intake of chow was measured, and the rats were weighed
just prior to stress to confirm that food intake and body weights did not
differ significantly, especially between the restriction-history groups
(R + NS and R + S). This was done to rule out the possibility that
overeating was due to energy deficiency from insufficient refeeding
following the days of caloric restriction.

Statistical Analyses

Between-subjects analyses of variance (ANOVA)s were used to assess
differences in body weight and food intake among groups immediately prior to
and during feeding tests, respectively. Sources of significant main effects were
assessed with Tukey’s honestly significant difference (HSD) post hoc tests.
Repeated measures ANOVA were used to determine differences in food-
take responses to drug treatments. Significant Drug × Group (D × G)
interactions were followed with Tukey’s HSD post hoc tests to assess differ-
ences among groups in the magnitude of drug-induced enhancement or sup-
pression of food intake relative to saline-induced responses. Chow and cookie
gram intakes were converted to kilocalories of intake and reported as cumu-
lagative group mean food intake in kilocalories ± SEM.

Results

Data presented in Figure 1 replicate the binge-eating-inducing
effects of restriction and stress reported in two previous studies
(Hagan et al., 2002, 2003). The intake of sated rats with a history of
caloric restriction alone and those subjected to stress alone did
not differ from that of nonrestriction, nonstress controls. However,
rats with a history of restriction, when subjected to stress by
footshock, ate 156.0% more HP kilocalories than did the three
other groups at 4 hr post-stress (Figure 1a). After 24 hr, the effect
of the earlier binge-eating episode was still evident, with R + S
rats eating 65.0% more kilocalories than the other groups (Fig-
ure 1b). This increase in intake was due to greater consumption of
HP food and was not accompanied by a compensatory decrease in
chow relative to other groups (Figures 1a and 1b). Increased
post-stress HP food intake was not due to hunger or energy deficit
carried over from the restriction–refeeding cycling, as evidenced
by the fact that, at the time of the stress-induced feeding test, the
rats did not differ in body weight (Figure 1c) or chow intake
(Figure 1d) during the previous day (Day 11 of cycle).

On the days of drug injections, baseline food intake (represent-
ing chow + HP food kilocalories consumed in the 2-hr period
immediately after time in the stress alley but just prior to drug
injections) was elevated in the R + S group versus the NR + S
group (46.1 ± 3.0 vs. 28.4 ± 3.0 kcal) prior to the naloxone test,
as well as in the R + S group versus the NR + S and NR + NS
groups (53.8 ± 4.0 vs. 37 ± 5.0 and 26.6 ± 2.0 kcal, respectively).
It is important to note that baseline consumption was not significa-
tively different between the two restriction-history groups prior to
injections with naloxone and butorphanol (R + S = 46.1 ± 3.0
and R + NS = 41.5 ± 3.0 kcal prior to naloxone; R + S = 53.8 ±
4.0 and R + NS = 48.3 ± 4.0 kcal prior to butorphanol).
However, as described below, these groups did respond differently
to the drugs.

In Figure 2, the saline bar graphs attest to the potent hyperphagia
of R + S rats on HP food despite an elevated baseline intake of
cookies prior to injection (not shown). When rats were given a
choice between HP food and chow, 1 mg/kg naloxone did not alter
chow intake after 2 hr, 4 hr, and 24 hr (hatched bars in Figures 2a,
2b, and 2c, respectively). An anorectic effect was apparent among

Figure 1. a: Mean 4-hr intake of chow and highly palatable (HP) food
(cookies) given together after the sixth restriction–refeeding cycle in rats
with a history of caloric restriction only (R + S) compared with that
of rats with stress only (NR + S), with a history of caloric restriction only
(R + NS), and with neither (NR + NS). b: Mean 24-hr intake of chow and
HP food given together after the sixth restriction–refeeding cycle in R + S
rats compared with that of NR + S rats, R + NS rats, and NR + NS rats.
c: Mean chow intake of all groups on the day prior to stress-induced
feeding test; no significant differences (ns). d: Mean body weight of all
groups immediately prior to stress-induced feeding test; no significant differences (ns). Error bars
represent standard error of the group’s mean. ***p < .001 difference in total
and in HP food intake versus other groups. ***p < .001 difference in total
and in HP food intake versus other groups.
Figure 2. Effect of 1 mg/kg ip opioid antagonist naloxone and saline on intake of chow and cookies (highly palatable [HP] food) when given as a choice after the 8th and 9th restriction–refeeding cycles in rats serving as controls (NR + NS), with stress only (NR + S), with a history of caloric restriction only (R + NS), or with a history of caloric restriction and stress (R + S) at 2 hr (a), 4 hr (b), and 24 hr (c) postinjection; no significant effect of naloxone within or between groups was observed for chow intake. Error bars represent standard error of the group’s mean. **p < .01 significant naloxone-induced suppression of HP food intake (% is percentage reduction of saline-treated HP food intake). ***p < .001 significant naloxone-induced suppression of HP food intake (% is percentage reduction of saline-treated HP food intake). *p < .05 saline-induced difference in HP food intake between R + S and R + NS group, ns with other two groups with Tukey’s honestly significant difference. +++ p < .001 difference in control HP food intake (that following saline injection) between R + S rats and all other groups. No asterisk = ns; Sal = saline; Nalx = naloxone.
In this study, naloxone exerted no significant anorectic effect in the three control groups but significantly suppressed intake in the R + S rats. Others and we have found that 1 mg/kg naloxone suppresses HP food intake in rats (Hagan et al., 1997; Shabir & Kirkham, 1999; Weldon et al., 1996). We used stringent post hoc tests, which increased the threshold for statistically significant suppression of intake, but a naturally higher threshold to reduce intake may have been set by an increased motivation for HP food

![Figure 3](image1.png)

**Figure 3.** Effect of 8 mg/kg ip opioid agonist butorphanol and saline on intake of chow and cookies (highly palatable [HP] food) when given as a choice after the 12th and 13th restriction–refeeding cycles in rats serving as controls (NR + NS), with stress only (NR + S), with a history of caloric restriction only (R + NS), or with both a history of caloric restriction and stress (R + S) at 2 hr (a), 4 hr (b), and 24 hr (c) following injection; no significant effect of butorphanol within or between groups was observed on chow intake. Error bars represent standard error of the group’s mean. *p < .05 significant butorphanol-induced stimulation of HP food intake (% is percentage increase of saline-treated HP food intake). **p < .001 significant butorphanol-induced stimulation of HP food intake (% is percentage increase of saline-treated HP food intake). ***p < .001 difference in control HP food intake (that following saline injection) between R + S rats and all other groups. No asterisk = ns; Sal = saline; Butr = butorphanol.

![Figure 4](image2.png)

**Figure 4.** Effect of 8 mg/kg ip opioid agonist butorphanol and saline on intake of chow when chow was the only choice available (no highly palatable food) after the 16th and 17th restriction–refeeding cycles, in rats serving as controls (NR + NS), with stress only (NR + S), with a history of caloric restriction only (R + NS), or with both a history of caloric restriction and stress (R + S) at 2 hr (a), 4 hr (b), and 24 hr (c) after stress; no difference between or within groups using Tukey’s honestly significant difference tests. Error bars represent standard error of the group’s mean.
produced by the rats’ limited access to this type of food prior to the drug tests. This may also explain why 8 mg/kg butorphanol, which has been found to increase food intake (Hagan & Moss, 1991; Levine, Grace, Portoghese, & Billington, 1994), did not do so in our control groups. To our knowledge, we are the first to test the effects of these drugs on feeding in rats cycled through such a schedule of intermittent access to HP food. We suspect that higher doses may have significantly altered intake in the control groups, whereas the exaggerated responses in the R + S group would have remained evident. Future full dose–response profiles of these drugs, especially of selective opioid-subreceptor (namely mu) agents, will elucidate neurochemical changes produced by cyclic food restriction and stress.

The increased potency of naloxone’s anorectic effects on binge eating (R + S) rats might be dismissed as an action of opioid blockade to reduce intake only because these rats were overeating to begin with. However, the fact that an agonist with affinity for the same mu and kappa subreceptors not only raised the ceiling on binge eating of HP food in these rats but did so with the highest degree of potency relative to the other groups argues for altered opioid regulation in these rats. Nonetheless, it will still be interesting to assess the response to these drugs while controlling for baseline intakes (e.g., elevating a control group’s intake to that of binge-eating rats via acute food restriction).

Current results also hint that sensitized opioid-receptor signaling may be necessary to initiate binge eating. The R + S rats typically did not compensate for the largest bout of binge eating, which was from 4 to 6 hr post-stress, because after 24 hr, their intake remained higher than controls’. We observed that when these rats were treated with naloxone, binge eating remained inhibited after 24 hr, when pharmacological actions of naloxone would be expected to have dissipated (Kirkham & Blundell, 1987; Levine & Morley, 1983; Ngai, Berkowitz, Yang, Hempstead, & Spector, 1976). Hence, if opioid-receptor signaling is blocked prior to binge eating, it may abolish the drive to binge altogether. The body of work on opioid regulation of feeding, however, weighs more heavily on a role of opioids to maintain, not initiate, feeding (Kirkham & Blundell, 1987; Rudski et al., 1997). If this is so, it is possible that the exaggerated anorectic response of binge-eating rats to naloxone was due to a more sustained level of HP food intake that developed in response to cyclic exposure to restriction and stress.

Caloric restriction in rats alters opioid expression (Berman, Devi, Spangler, Kreek, & Carr, 1997) and receptor binding (Tsujii et al., 1986; Wolinsky, Carr, Hiller, & Simon, 1994), but this alone cannot explain the enhanced anorectic and orexigenic response of binge-eating rats to the opioid treatments because rats with a history of restriction but no stress (R + NS) did not respond in kind. Even if the R + S rats incurred persistent physiological changes common to deprived (hungry) animals, the effects of opioid drugs in food-restricted rats would be expected to be attenuated, not enhanced, as reported by others (Glass, Grace, Cleary, Billington, & Levine, 1996; Sanger & McCarthy, 1982).

Very little is known regarding the persistence of physiological changes, if any, to cycles of food restriction and refeeding. Mary M. Boggiano (formerly Mary M. Hagan) found that female rats with similar cycles of restriction, despite a return to normal body weight and food intake, responded supersensitively to the orexigenic action of 8 mg/kg butorphanol (Hagan & Moss, 1991). Hence, a history of caloric restriction alone may increase vulnerability to binge eating by altering opioid-receptor function.

Like a history of caloric restriction, the presence of HP food also appears critical to binge eating. HP feeding stimulates opioid release in the hypothalamus (Dum, Gramsch, & Herz, 1983; Welch, Kim, Grace, Billington, & Levine, 1996) and may explain why, in previous R + S rats, just a taste-sized morsel of HP food was able to unleash binge eating of chow, a less preferred food, an effect that did not occur without the HP food trigger (Hagan et al., 2003). Exposure to HP food after bouts of food restriction may also explain why only those rats with access to HP food after bouts of caloric restriction, versus rats without HP food after restriction, continued to overeat HP food well after cessation of the restriction cycles (Hagan & Moss, 1997). Hence, in this protocol, stress may render R + S rats vulnerable to binge, but it is HP food, possibly via release of endogenous opioids (as we artificially manipulated with butorphanol), that acts as the real binge trigger.

Substituting an injection of butorphanol for a morsel of HP food did not mimic the latter’s ability to trigger a binge on regular rat chow as previously observed (Hagan et al., 2003). Whether or not a receptor-selective agonist can act to trigger binge eating of a less palatable food like chow needs to be determined. It is the hedonic properties of HP food that may sufficiently activate an altered opioid system to unleash binge eating. This is supported by sham-feeding experiments in which naloxone attenuated food intake (Kirkham, 1990; Leventhal, Kirkham, Cole, & Bodnar, 1995), proving that oerosensory, and not postdigestive, factors are sufficient for its anorectic actions. Although not yet specifically investigated, a sensitized opioid system may underlie the common clinical observation that just a bite of HP (often forbidden) food triggers binges and makes it difficult to abstain from binge eating (Abraham & Beumont, 1982; Hetherington & Rolls, 1991). This is not an unrealistic inferential leap to humans given that, similar to our results in rats, naloxone reduced total caloric intake of snack food relative to baseline in binge eaters but not in controls and that, as also evident in our rats, the reduction was most pronounced for sweet high-fat foods such as cookies and chocolate (Drewnowski, Krahn, Demitrack, Nairn, & Gosnell, 1992).

Maintenance on HP diets and access to HP food following injection have been shown to increase rats’ sensitivity to the anorectic actions of naloxone and naltrexone (Glass et al., 1996; Kirkham, 1990; Rudski et al., 1997; Shabir & Kirkham, 1999; Tsujii et al., 1986; Yeomans & Clifton, 1997). However, because all of our groups were maintained on a feeding regimen that included the same amount of HP food access, this alone cannot explain why the R + S rats had a greater anorectic response to naloxone’s effects. Recent findings in studies subjecting rats to intermittent access to HP food may be more relevant to the mechanisms underlying binge eating in our model. Some of these findings include reduced enkephalin gene expression (Kelley et al., 2003; Spangler et al., 2004) and increased mu1-receptors (Colantuoni et al., 2001) in mesolimbic nuclei critical to reward, as well as naloxone-induced precipitation of opiate withdrawal symptoms (Colantuoni et al., 2002), all occurring in rats on schedules of intermittent access to HP food. Although there is no energy deficit encumbered by these schedules, the rats may have been in a “hedonic deprivation state” (Levine & Billington, 2004, p. 59). The physiology of this state may be similar to that adapted from cyclic caloric restriction including intermittent HP food as experienced by the R + S rats. In fact, an alternate but compelling...
expected the R group to overeat as much as R + S rats, but they did not. However, future experiments should test whether there is an interaction between diestrous cycle and stress to evoke binge eating. In regard to the effect of radical changes in circadian rhythms on food intake, we have been able to replicate the binge eating in R + S rats when the food is provided immediately after lights out, instead of lights on (unpublished data). Therefore, the binge eating imposed by restriction and stress does not appear to be affected by changes incurred from shifts in circadian rhythm. We believe that an animal model of binge eating should be robust to possible restriction-induced changes in circadian rhythms and reproductive hormones because, in human binge-eating disorders, binge eating can and does occur at unusual times (as in late-night binge eating) and in amenorrheic patients (American Psychiatric Association, 1994; Grilo & Masheb, 2004).

We propose that binge eating is an adaptive response to abnormal environmental conditions. The fact that bouts of caloric restriction and stress, which alone are not sufficient to produce changes in food intake, together induce binge eating in rats attests to the strong influence of these environmental factors on feeding behavior. The differential and strikingly exaggerated response of binge-eating rats to naloxone and butorphanol implicates opioids in the neurochemistry of dieting- and stress-induced binge eating. Opiate antagonists have been implicated as treatments for bulimia and binge-eating disorder, but only limited tests have been conducted, and these have been restricted to the use of mixed antagonists, namely, naloxone and naltrexone (Drewnowski, Krah, Demitrack, Nairn, & Gosnell, 1995; Marrazzi, Kinzie, & Luby, 1995). Defining the exact opioid proteins, receptors, and neural regions involved in binge eating promises to introduce new and more targeted opioid treatments for these disorders. Other novel pharmacological treatments may involve CNS signals found to interact with opioids to affect binge eating and intake of palatable food. Central peptide YY, the melanocortin 4 receptor, and GABA (Branson et al., 2003; Hagan, 2002; Hagan et al., 2001; Will, Franzblau, & Kelley, 2004) are candidates that may prove particularly efficacious in the treatment of binge-eating disorders.

References

Kelley, A. E., Will, M. J., Steinenber, T. L., Zhang, M., & Haber, S. N. (2003). Restricted daily consumption of a highly palatable food (choco-
olate Ensure) alters striatal enkephalin gene expression. European Jour-
nal of Neuroscience, 18, 2592–2598.
sham feeding 30% sucrose: Reversal by repeated naloxone administra-
Kirkham, T. C., & Blundell, J. E. (1987). Effects of naloxone and naltrex-
one on meal patterns of freely-feeding rats. Pharmacology Biochemistry
and Behavior, 25, 515–520.
Selective actions of central mu and kappa opioid antagonists upon
Levine, A. S., & Billington, C. J. (2004). Opioids as agents of reward-
related feeding: A consideration of the evidence. Physiology & Behav-
or, 82, 57–61.
effect of selective opioid antagonists on butorphanol-induced feeding.
in rats. Life Sciences, 32, 781–785.
analysis on the use of naltrexone in the treatment of bulimia. Interna-
tional Clinical Psychopharmacology, 10, 173–176.
Characteristics of 275 patients with bulimia. American Journal of Psychi-
try, 142, 482–485.
Ngai, S. H., Berkowitz, B. A., Yang, J. C., Hempstead, J., & Spector, S.
(1976). Pharmacokinetics of naloxone in rats and in man: Basis for its
maintenance diet increases sensitivity to appetite suppressant effects
is attenuated by adaptation to a food-deprivation schedule. Psychophar-
macology (Berlin), 77, 336–338.
Shabir, S., & Kirkham, T. C. (1999). Diet-induced enhancement of nalox-
one sensitivity is independent of changes in body weight. Pharmacology
Spangler, R., Wittkowski, K. M., Goddard, N. L., Avena, N. M., Hoebel,
expression in reward areas of the rat brain. Brain Research. Molecular
Brain Research, 124, 134–142.
onset in adolescent girls: A 2-year prospective investigation. Health
Psychology, 21, 131–138.
(1986). Effects of food deprivation and high fat diet on opioid receptor
Welch, C. C., Kim, E. M., Grace, M. K., Billington, C. J., & Levine, A. S.
(1996). Palatability-induced hyperphagia increases hypothalamic dynor-
Welldon, D. T., O’Hare, E., Cleary, J., Billington, C. J., & Levine, A. S.
(1996). Effect of naloxone on intake of cornstarch, sucrose, and polycose
diets in restricted and nonrestricted rats. American Journal of Physiol-
ogy, 270, R1183–R1188.
critical for opioid-mediated binge-eating of fat. NeuroReport, 15, 1857–
1860.
of chronic food restriction on mu and kappa opioid binding in rat forebrain:
enhances the anorectic effect of naloxone but not d-fenfluramine. Phys-
iology & Behavior, 62, 255–262.

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