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Feeding, Drug Abuse, and the Sensitization of Reward by Metabolic Need*

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The incentive-motivating effects of external stimuli are dependent, in part, upon the internal need state of the organism. The increased rewarding efficacy of food as a function of energy deficit, for example, has obvious adaptive value. The enhancement of food reward extends, however, to drugs of abuse and electrical brain stimulation, probably due to a shared neural substrate. Research reviewed in this paper uses lateral hypothalamic electrical stimulation to probe the sensitivity of the brain reward system and investigate mechanisms through which metabolic need, induced by chronic food restriction and streptozotocin-induced diabetes, sensitizes this system. Results indicate that sensitivity to rewarding brain stimulation varies inversely with declining body weight. The effect is not mimicked by pharmacological glucoprivation or lipoprivation in ad libitum fed animals; sensitization appears to depend on persistent metabolic need or adipose depletion. While the literature suggests elevated plasma corticosterone as a peripheral trigger of reward sensitization, sensitization was not reversed by meal-induced or pharmacological suppression of plasma corticosterone. Centrally, reward sensitization is mediated by opioid receptors, since the effect is reversed by intracerebroventricular (i.c.v.) infusion of naltrexone, TCTAP (μ antagonist) and nor-binaltorphimine (κ antagonist). The fact that these same treatments, as well as i.c.v. infusion of dynorphin A antiserum, block the feeding response to lateral hypothalamic stimulation suggests that feeding and reward sensitization are mediated by a common opioid mechanism. Using in vitro autoradiography, radioimmunoassays and a solution hybridization mRNA assay, brain regional μ and κ opioid receptor binding, levels of prodynorphin-derived peptides, and prodynorphin mRNA, respectively, were measured in food-restricted and diabetic rats. Changes that could plausibly be involved in reward sensitization are discussed, with emphasis on the increased dynorphin A_{1-8} and prodynorphin mRNA levels in lateral hypothalamic neurons that innervate the pontine parabrachial nucleus, where μ binding decreased and κ binding increased. Finally, the possible linkage between metabolic need and activation of a brain opioid mechanism is discussed, as is evidence supporting the relevance of these findings to drug abuse.

KEY WORDS: Opioid; reward; dynorphin; food restriction; drug abuse.

INTRODUCTION

An increasingly well-supported model in the neurobiology of drug abuse holds that the rewarding effects of drugs result from activation of neural circuits that mediate incentive-motivating effects of food (1,2). Numerous studies provide evidence of the co-regulation of feeding and drug responses. For example, the locomotor response to amphetamine and the self-administration of morphine can both be predicted by an animal's propensity to ingest a sweet solution (3,4). Moreover, for virtually every known drug of abuse, food-satiation

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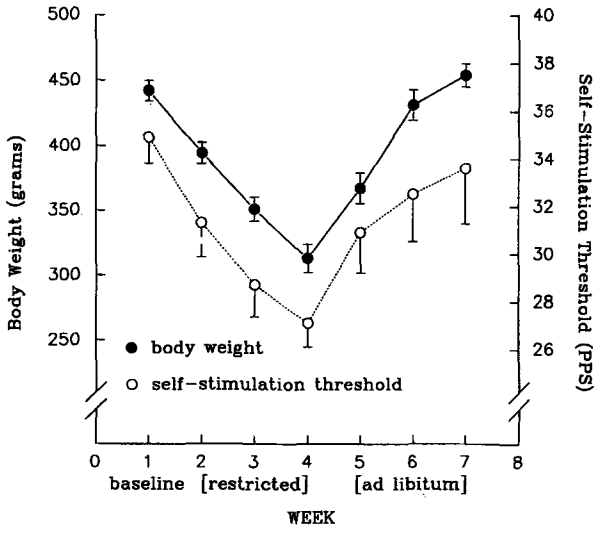

Fig. 1. Lateral hypothalamic self-stimulation (LHSS) thresholds were monitored in nine rats throughout a 7-week experiment that included 1 week of baseline testing, 3 weeks of food restriction (approximately 40% *ad libitum* intake) and 3 weeks of ad libitum refeeding. Weekly mean ± SEM bodyweights and LHSS thresholds are plotted separately as a function of experimental weeks. From Carr and Wolinsky (29), with kind permission of Elsevier Science Ltd.

diminishes while food restriction enhances self-administration (5). Most significantly, food-restricted animals self-administer lower doses of cocaine, morphine and other drugs than would reinforce responding in ad libitum fed animals. Extensive behavioral analyses by Carroll and coworkers indicate that food restriction specifically increases the reinforcing efficacy of abused drugs (5). Although experimental testing has been limited, a relationship between food and drug motivation has also been observed in humans (6). Clinically, a high comorbidity of eating disorders and substance abuse has been documented (7).

Neurobiological investigations support the hypothesis that reinforcing effects of food and drugs are mediated by related neural circuits, with most research focused upon mesolimbic dopamine neurons as a "final common pathway" (1,2,8). Over the years, one of the most productive approaches to investigating the neurobiology of reward has involved the use of medial forebrain bundle (mfb) electrical stimulation. Self-stimulation (LHSS) in the lateral hypothalamic mfb interacts with drugs and food in a way that is consistent with mediation by a common neural substrate. For example, all drugs of abuse decrease the threshold for LHSS (9,10) while withdrawal from cocaine and morphine increase the threshold (11,12). Sweet solution infused into the oral cavity decreases the threshold (13) while force-feeding to super-satiety increases the threshold (14). The facilitatory effect of exogenous opiates on LHSS has been attributed to sites of action within the ventral tegmentum (15) and nucleus accumbens (16). The facilitatory effects of psychostimulants have also been localized to nucleus accumbens (17). The sites in which these drugs act to facilitate LHSS are the very sites supporting intracerebral self-administration (18,19,20) and place preference conditioning (21,22). The relationship between drug reward, LHSS and feeding is underscored by the fact that opiate and psychostimulant microinjections in these same loci stimulate food intake (23,24), as does LH electrical stimulation itself.

One of the essential characteristics of appetitive motivation is that the incentive effects of external stimuli are regulated by the internal need state of the organism (25). It is well-documented that the hedonic response to food taste is enhanced by food-restriction (26,27). As might be expected from the foregoing discussion of overlapping neural substrates, the enhancement of reward by food restriction extends to drugs of abuse (5) and LHSS (28,29). Thus, elucidation of brain mechanisms that regulate incentive effects of food may not only advance the neurobiology of adaptive behavior but possibly also suggest physiological factors that predispose eating disorders and drug abuse. For this reason, our laboratory has used electrical brain stimulation paradigms to investigate sensitization of the brain reward system by metabolic need states.

BEHAVIORAL STUDIES

Sensitizing Effect of Chronic Food Restriction on Brain Stimulation Reward. In the first experiment to be described, rats with chronically indwelling LH electrodes were trained to leverpress for 1-sec duration trains of cathodal square-wave stimulation. A 'method of limits' was used to measure the LHSS threshold, defined as the minimum brain stimulation frequency needed, at fixed current, to support a response rate of 15 leverpresses per minute. Thresholds were monitored over days and their stability was established. When subjects were then placed on a three week regimen of food restriction, with food access limited to a single 1-hour period per day, LHSS thresholds and body weights declined together (29). The decrease in LHSS threshold during food restriction was present whether rats were tested prior to or following the daily meal (30) and returned to baseline only gradually, over days, after ad libitum access to food was restored (Fig. 1).

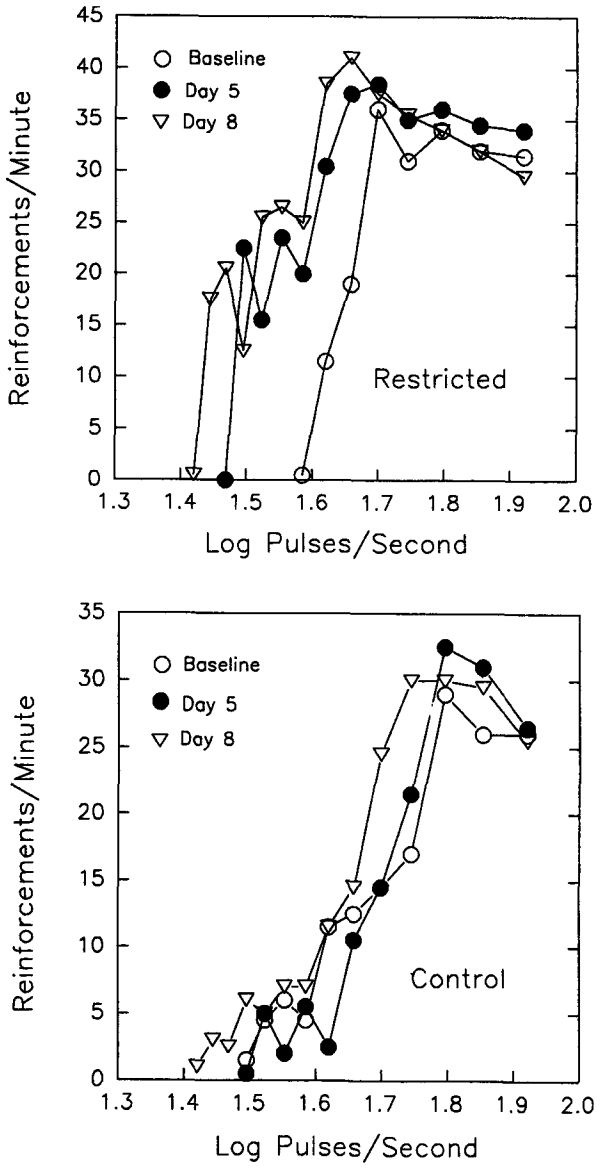

Fig. 2. Rate-frequency curves for a representative food-restricted rat (top) and ad libitum fed control rat (bottom) are displayed. In each case, the number of reinforced leverpresses per minute is plotted as a function of the lateral hypothalamic log pulse stimulation frequency delivered. The restricted rat was tested on days 5 and 8 of the food restriction regimen. The rate-frequency curves obtained on these days are compared with that obtained under baseline (*ad libitum*) conditions prior to food restriction. From Abrahamsen, Berman and Carr (30), with kind permission of Elsevier Science Ltd.

To achieve a more comprehensive analysis of the effect of food restriction on LHSS, a psychophysical curve-shift method was used to explicitly differentiate effects of food restriction on brain stimulation rewarding efficacy and performance (30). This method relates changes in LHSS response rate to systematic changes in brain stimulation frequency, yielding a function comparable to the pharmacological dose-response curve. Food restriction consistently shifted rate-frequency curves to the left, lowering the M-50 (threshold for 50% maximum response rate) and Theta-O (X-intercept) parameters of rewarding efficacy (Fig. 2). These changes are indicative of a sensitized reward substrate and are precisely the effects produced by drugs of abuse (15,17,31,32). Changes in maximum response rates and slopes of rate-frequency functions are characteristic of treatments that alter performance variables such as motor capability and arousal; food restriction had no effect on these parameters. Thus, chronic food restriction sensitizes the brain reward system, producing effects comparable to drugs of abuse. The neuroanatomical sites within which drugs of abuse act to facilitate LHSS are known (see above). Identification of the sites and neurochemical mediators through which food restriction achieves this effect are among the goals of the work to be described below.

Effects of Glucoprivic and Lipoprivic Agents in ad Libitum Fed Animals. Hyperphagia and an interoceptive state equivalent to food deprivation can be induced by administering 2-deoxy-D-glucose (2-DG) to ad libitum fed animals (33–35). This compound competitively antagonizes the phosphohexose isomerase step of glycolysis and thereby produces acute cellular glucopenia. Nicotinic acid blocks the mobilization of free fatty acids from adipose tissue and interacts synergistically with 2-DG in decreasing the metabolic rate and producing a robust and sustained eating response (36,37). To determine whether signals generated by acute tissue need are likely to underlie the sensitization of reward, these treatments were administered to ad libitum fed animals and effects on LHSS rate-frequency curves were determined (Cabeza de Vaca and Carr, in preparation). 2-DG alone, at a dose of 200 mg/kg, produced a 2-fold compensatory increase in blood glucose levels but failed to affect LHSS. This result confirms a prior finding (38). Nicotinic acid alone, at a dose of 250 mg/kg, which produces a nearly complete suppression of plasma free fatty acids (39), also failed to affect LHSS. Combined treatment, which stimulates a pronounced feeding response (36,37), also failed to affect LHSS. It therefore seems that the internal signals that stimulate food intake in the short term do not sensitize reward. Reward sensitization may instead be dependent upon metabolic or hormonal adaptations that develop over a sustained period of energy deficit or adipose depletion.

Evaluation of Plasma Corticosterone Involvement in Reward Sensitization. The hypothesis that persistent metabolic need or adipose depletion is the trigger of re-

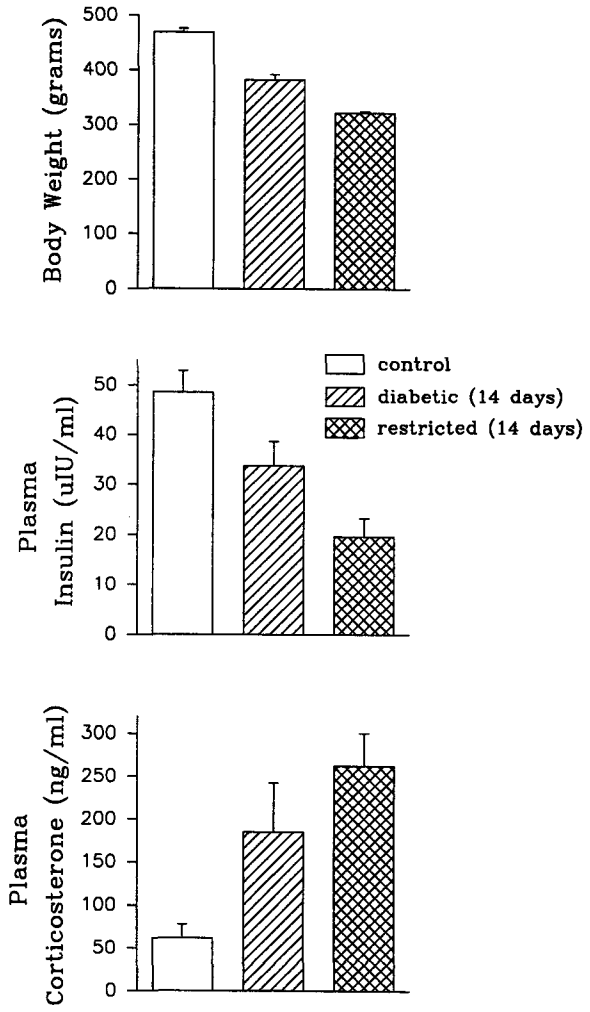

Fig. 3. Three groups, containing 10 rats each, were matched for initial body weight and subject to either a continuation of ad libitum feeding, food-restriction consisting of daily access to a single 10-gram meal, or injection of streptozotocin (50 mg/kg, i.p.). Two weeks later, rats were sacrificed for brain extraction and trunk blood was collected. Plasma levels of insulin and corticosterone were determined using ^{125}I-radioimmunoassay kits. Final mean (± SEM) body weights, plasma insulin and corticosterone are displayed for control, food-restricted and diabetic rats. From Berman and Carr (previously unpublished).

ward sensitization is supported by the finding that streptozotocin-induced diabetes also produces a decline in the LHSS threshold (40). Peripheral physiological adaptations that are common to food restriction and diabetes, such as increased plasma corticosterone and decreased plasma insulin, are therefore under investigation as possible antecedents to the sensitization of brain reward (Fig. 3).

One of the primary functions of corticosterone is to assure adequate supplies of energy and mobilizable glucose (41). Thus, both food-restricted and untreated diabetic rats display elevated corticosterone levels. In restricted rats, mean daily corticosterone levels are strongly negatively correlated with the amount of food eaten (42). These elevated levels would be expected to alter CNS functions since circulating corticosterone crosses the blood-brain barrier and binds to intracellular receptors (43). Moreover, Piazza and coworkers have demonstrated that the locomotor activating effects of morphine, amphetamine and cocaine covary with plasma corticosterone levels (44–46). Most germane to the present work is their finding that rats food-restricted to 80% body weight show a potentiated locomotor response to morphine and amphetamine but not if they have been adrenalectomized and implanted with a subcutaneous corticosterone pellet to stabilize plasma levels (45). Recently, the same investigators reported that the potentiated locomotor response to cocaine in food-restricted rats could be reversed by metyrapone, an inhibitor of corticosterone synthesis (47).

The involvement of corticosterone in the sensitization of reward by food restriction was therefore investigated in two ways. First, we exploited the fact that plasma corticosterone levels peak immediately prior to the daily meal and decline precipitously in the post-meal period. While post-meal corticosterone levels did in fact decline to levels observed in ad libitum fed rats, the sensitization of reward was unchanged. Thus, LHSS thresholds did not vary with dynamic changes in plasma corticosterone (30). To pursue this issue further, a second study was conducted in which corticosteroid synthesis inhibitors were used to suppress plasma corticosterone. Both aminoglutethimide, which blocks the initial step in the adrenocorticoid biosynthetic pathway, and metyrapone, which blocks the final step in corticosterone synthesis, were given to food-restricted rats and the time-course of plasma corticosterone suppression was evaluated (Fig. 4). Behavioral tests, which were timed to coincide with each drug's peak suppression of corticosterone, revealed that neither drug reversed the sensitization of reward by food restriction (48) (Fig. 5). Thus, unlike the sensitizing effect of food restriction on the locomotor stimulating effect of cocaine, the sensitization of LHSS is not reversed by an acute suppression of corticosterone.

Involvement of Brain Opioid Receptors in Reward Sensitization. The central mechanisms of reward sensitization have been shown to involve opioid receptors. When repeated measurements were taken on a group of rats under ad libitum and restricted access feeding conditions, intracerebroventricular (i.c.v.) infusions of naltrexone selectively increased the LHSS threshold during food restriction (29) (Fig. 6). Similarly, when rats ren-

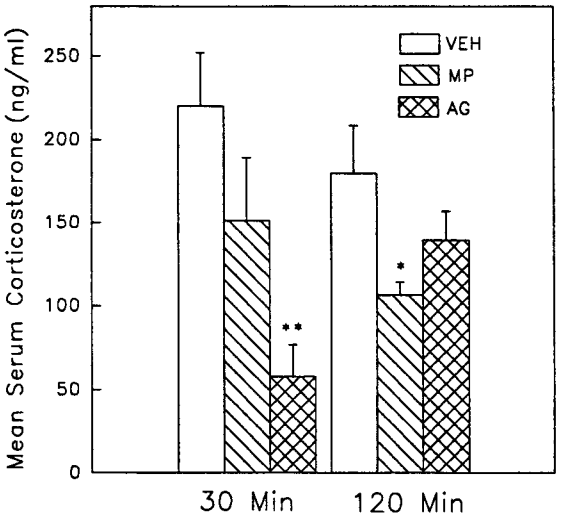

Fig. 4. Mean (± SEM) serum corticosterone levels (ng/ml) are displayed for blood samples taken from the tail vein 30 and 120 minutes following vehicle (open bars), 100 mg/kg metyrapone (MP; single hatched bars) and 50 mg/kg aminoglutethimide (AG; cross hatched bars) in food-restricted rats. Measurements were taken on 5 rats per group. *$p < .05$, **$p < .01$ as compared to control. From Abrahamsen and Carr (48), with kind permission of Elsevier Science Ltd.

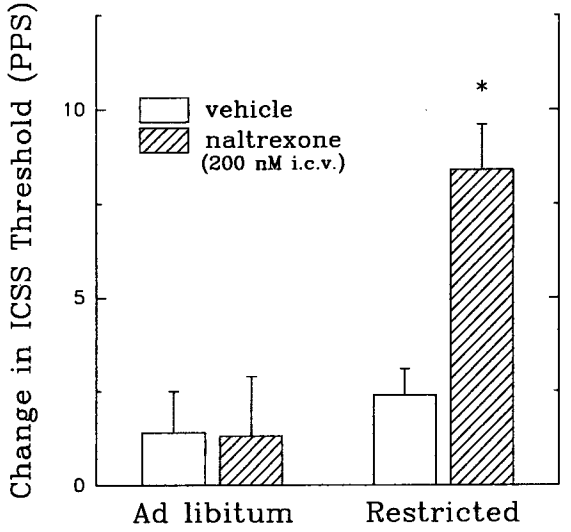

Fig. 6. LHSS thresholds following lateral ventricular injection of naltrexone (200.0 nmol) or vehicle are expressed as mean (± SEM) change from the preinjection thresholds, expressed in pulses per second (PPS), obtained the same day. Six rats were tested under *ad libitum* and restricted feeding conditions. From Carr and Wolinsky (29), with kind permission of Elsevier Science Ltd.

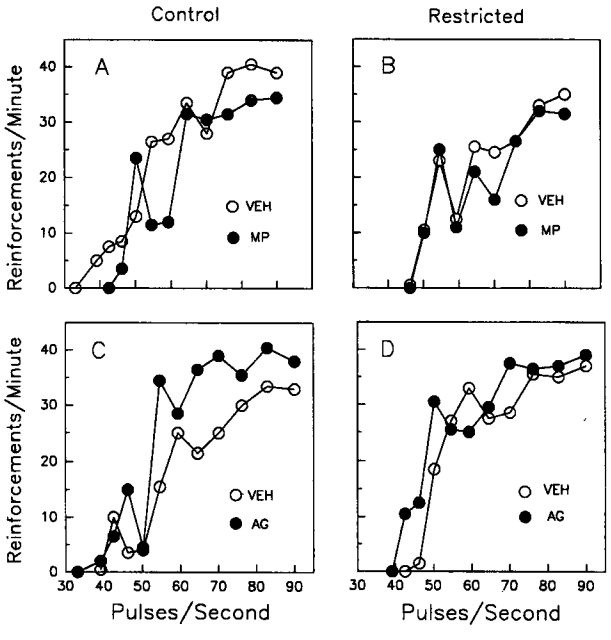

Fig. 5. LHSS rate-frequency curves for representative food-restricted (panels B and D) and ad libitum fed control rats (panels A and C). Displayed are data collected following the administration of metyrapone (MP; 100 mg/kg, 60 min prior to testing; top panels) and aminoglutethimide (AG; 50 mg/kg, 15 min prior to testing; bottom panels) and corresponding vehicles. In each case, number of reinforced leverpresses per minute is plotted as a function of the LH stimulation frequency in pulses per second. Based upon results reported by Abrahamsen and Carr (48).

dered diabetic by streptozotocin were given naltrexone, their LHSS thresholds returned to pre-diabetic values (40). These findings suggest that metabolic need states sensitize the reward system by triggering an opioid mechanism that is otherwise inactive.

Receptor-selective antagonists were then used to investigate the involvement of multiple opioid receptor types (49). For each antagonist, separate groups of ad libitum fed and food-restricted rats were used to conduct i.c.v. dose-response studies. In restricted rats, drugs were administered during the second and third weeks of the feeding regimen. Both the μ antagonist, TCTAP, and the κ antagonist, norbinaltorphimine, selectively raised the LHSS threshold of food-restricted rats while the δ antagonist, naltrindole, did not (Fig. 7). This suggests that both μ and κ receptors are involved in the sensitization of reward. The possibility that this opioid mechanism facilitates drug self-administration is supported by the finding that food-restricted animals self-administer previously subrewarding doses of cocaine, but not if they are pretreated with naltrexone (50).

The Possible Relation Between Opioid Mechanisms that Sensitize Reward and Mediate Feeding. The opioid mechanism that facilitates LHSS may be closely related to that which mediates feeding itself. LH stimulation that is below threshold for LHSS often elicits feeding. This feeding is inhibited by naltrexone (51), TCTAP, norbinaltorphimine (52) and dynorphin A antiserum (53) (Figs.

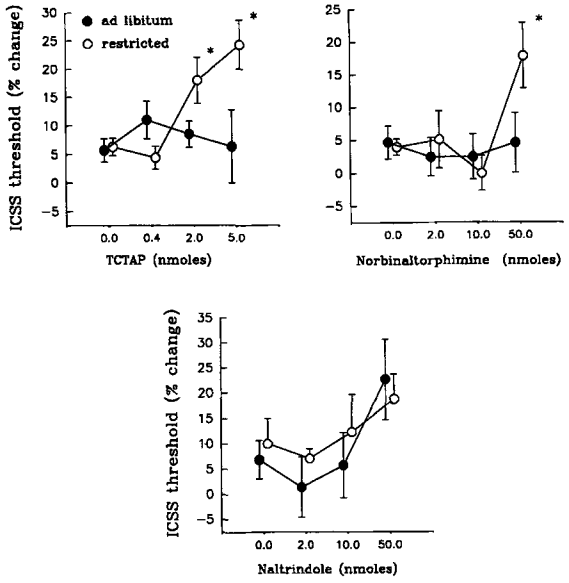

Fig. 7. Self-stimulation (ICSS) thresholds following vehicle and three receptor type-selective antagonists were determined in six separate groups (n = 4) of ad libitum fed and food-restricted rats and expressed as the percentage change from the preinjection value. Mean (± SEM) changes in threshold are plotted above as a function of lateral ventricular dose of TCTAP (μ antagonist, top left; *p < .01), nor-binaltorphimine (κ antagonist, top right; *p < .05) and naltrindole (δ antagonist, bottom). From Carr and Papadouka (49), with kind permission of Elsevier Science Ltd.

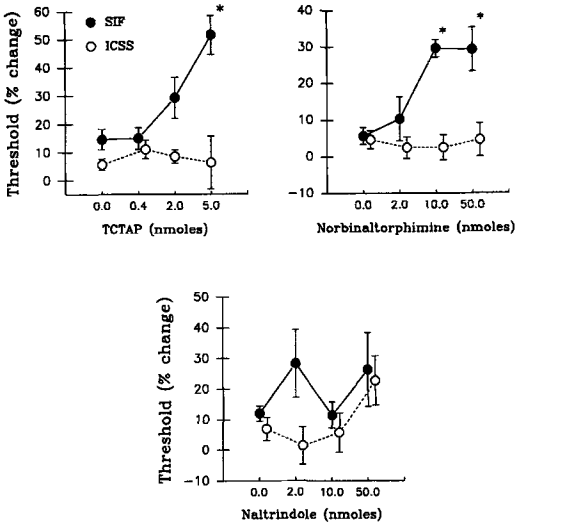

Fig. 8. Six separate groups of ad libitum fed rats were used to determine effects of receptor type-selective opioid antagonists on the threshold for lateral hypothalamic stimulation-induced feeding (SIF) and self-stimulation (ICSS). SIF thresholds were defined as the minimum stimulation frequency required to elicit 5 seconds continuous eating of wet mash at a latency no greater than 20 seconds from stimulation onset. A method of limits as described for measurement of ICSS thresholds (see text) was used. Thresholds obtained in postinjection tests are expressed as mean (± SEM) percentage change in relation to preinjection means and plotted as a function of the intracerebroventricular dose administered. Top left: Effects of TCTAP (μ antagonist) on SIF (n = 6) and ICSS (n = 4). *p < .01. Top right: Effects of nor-binaltorphimine (κ antagonist) on SIF (n = 4) and ICSS (n = 4). *p < .01. Bottom: Effects of naltrindole (δ antagonist) on SIF (n = 8) and ICSS (n = 4). Adapted from Papadouka and Carr (52), with kind permission of Elsevier Science Ltd.

8 & 9). Extensive behavioral analyses conducted in these animals suggest that anti-opioid treatments inhibit feeding by blocking the rewarding effect of food taste (54). This conclusion is supported by the effects of opioid antagonists in taste reactivity, taste preference, palatability-induced hyperphagia, and sucrose sham-feeding paradigms (55–59).

Thus, there is a parallel between results of the feeding and LHSS studies just outlined. In both cases, opioid transmission has been inferred to promote responding by facilitating the incentive effect of a stimulus. Moreover, in both cases the opioid facilitation of responding has been reduced by naltrexone, TCTAP and nor-BNI. This raises the possibility that food taste and metabolic need are separate triggers of a common opioid mechanism. If so, this opioid mechanism would serve a modulatory, rather than a mediating, function in relation to incentive motivation; energy deficit, by itself, is not likely to be a rewarding event but, rather, one that sensitizes the reward system to appropriate environmental stimuli (or electrical stimuli that supersede the normal afferent pathway but precede the point in the circuitry where opioid modulation occurs).

Aversive and Rewarding Effects of Dynorphin Peptides and κ Receptors. The suggestion that dynorphin and κ receptors play a positive role in reward function is contrary to much current thinking. κ agonists produce conditioned place aversions rather than preferences (60,61) and inhibit dopamine release in nucleus accumbens (62,63). However, there have been reports of i.c.v. (64) and intra-hippocampal (65) dynorphin self-administration as well as anxiolytic effects of κ agonists (66). Most importantly, while there is ample evidence that κ receptors inhibit transmission in the dopaminergic 'final common pathway' for incentive motivation, there is similarly ample evidence that dynorphin and κ receptors facilitate ingestion and do so by facilitating the incentive effects of palatable food taste (67–70). Separate, site-specific, functions of κ receptors would explain the curious observation that systemic doses of U50,488H (κ agonist) that produce a conditioned place aversion, also stimulate food intake (Papadouka and Carr, unpublished). This observation was made in a place conditioning study in which one of two distinctive compartments was repeatedly paired with U50,488H while the other was paired with saline. Half of all subjects had access

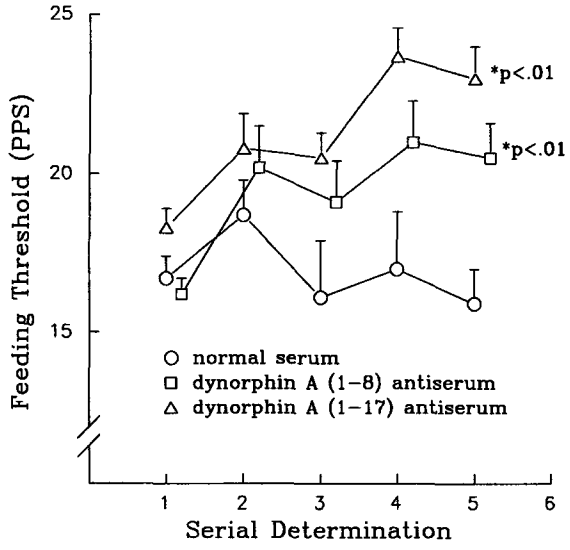

Fig. 9. Five determinations of the threshold for lateral hypothalamic stimulation-induced feeding were obtained in serial order during a 20-30 minute postinjection test using a method of limits. Repeated measurements were made on 10 rats tested 2 hours after lateral ventricular infusion of antibodies to dynorphin A_{1-8}, dynorphin A_{1-17} and normal rabbit serum control. Thresholds are expressed as mean (± SEM) brain stimulation frequency in pulses per second (pps). Adapted from Carr and Bak (53).

Table I. Effects of U50,488H on Place Aversion Learning and Food Intake

Dose (mg/kg)	% Place Aversion* (w/o food)	% Place Aversion (w/food)	Intake high fat mash (grams)
0	—	—	4.6
0.75	26%	20%	10.3
1.50	63%	34%	11.2

$$* \frac{\text{saline (sec)} - \text{drug (sec)}}{\text{saline (sec)} + \text{drug (sec)}} \times 100 = \% \text{ place aversion}$$

to a high fat mash during each of their daily 45-min conditioning trials and half did not. On the day of preference testing, rats displayed a clear aversion for the U50,488H-paired compartment despite the fact that the drug had markedly increased food intake during the conditioning trials (Table I). An interesting aside, is that rats that ate during conditioning trials displayed a weaker place aversion than rats that were conditioned without food. Whether eating ameliorates the aversive effect of U50,488H or simply distracts the animals and interferes with conditioning is not clear. Nevertheless, while the net effect of systemically administered κ agonists may be aversive, this effect co-exists with a selective enhancement of feeding. In physiological circuits, the motivational-affective function of dynorphin release and/or κ receptor stimulation is likely to vary with behavioral context and neuroanatomical locus.

STUDIES OF BRAIN OPIOID BINDING, PEPTIDE LEVELS, AND GENE EXPRESSION

Brain Regional Levels of μ and κ Opioid Receptor Binding. One approach to testing the hypothesis that a common opioid mechanism underlies feeding and reward sensitization would be to localize changes in opioid transmission that accompany chronic food restriction and conduct follow-up studies that target specific receptor types and/or peptides within discrete anatomical sites. In an effort to localize and characterize these changes, studies of brain regional opioid binding, dynorphin peptide levels, and prodynorphin gene expression have been carried out.

If chronic food restriction is accompanied by a change in tonic peptide release, compensatory changes might develop at the level of the binding site. Following reports that 72 hour food deprivation alters [^{3}H]-naltrexone and [^{3}H]dynorphin A_{1-8} binding in brain homogenates (71,72), we conducted an autoradiographic analysis of μ and κ receptor binding in food-restricted rats (73,74). Rats were subject to two weeks of food restriction and sacrificed at mealtime on the final day. Binding was carried out on slide-mounted brain sections in vitro using [^{3}H]DAGO to label μ receptors and [^{3}H]bremazocine, in the presence of excess DAGO and DPDPE to block μ and δ receptors, to label κ receptors. More than fifty brain regions, from medial prefrontal cortex to the nucleus solitarius, were analyzed and only six structures displayed changes in binding. μ binding was decreased in the basolateral/basomedial amygdala, parabrachial nucleus and habenula. κ binding was also decreased in the habenula but increased in the bed nucleus of the stria terminalis, ventral pallidum, medial preoptic area and parabrachial nucleus (Table II). Several of these changes are also present in streptozotocin-treated diabetic rats (Wolinsky, Abrahamsen and Carr, in preparation).

While the opioid release that facilitates LHSS during food restriction need not cause adaptive changes in receptor binding, the changes that were observed suggest that these structures have been subject to altered exposure to opioids. Since saturating concentrations of ^{3}H-ligands were used, the changes in binding may reflect changes in receptor density, which are typically thought to occur as a compensatory response to altered availability of endogenous ligand (75). Down-regulation is generally expected to occur in response to increased li-

Table II. Brain Regional Levels of μ and κ Opioid Receptor Binding

Brain Region	[^{3}H]DAGO (fmol/mg tissue)		[^{3}H]BMZ (fmol/mg tissue)	
	Ad libitum	Restricted	Ad libitum	Restricted
Bed n. stria terminalis				
medial anterior	39.0 ± 2.8	41.4 ± 7.6	28.5 ± 1.6	**38.2 ± 1.6***
lateral dorsal	22.8 ± 0.8	27.5 ± 3.0	21.6 ± 1.4	**29.1 ± 2.1***
ventral	28.2 ± 0.8	32.5 ± 3.1	28.2 ± 1.1	**43.1 ± 1.7***
Ventral pallidum	34.4 ± 1.1	38.4 ± 3.3	25.9 ± 0.7	**36.0 ± 3.0***
Medial preoptic area	33.6 ± 1.7	36.8 ± 1.5	39.1 ± 1.9	**62.3 ± 2.1***
Habenula				
medial	53.2 ± 1.5	**44.0 ± 7.3***	48.4 ± 5.1	**35.1 ± 2.9***
lateral	48.8 ± 1.0	**42.1 ± 3.1***	28.8 ± 3.5	26.0 ± 2.0
Amygdala				
basolateral	83.3 ± 2.8	**72.2 ± 4.1***	34.6 ± 4.0	33.3 ± 2.9
basomedial	43.0 ± 1.5	**37.3 ± 1.4***	22.8 ± 1.6	21.8 ± 1.6
Parabrachial nucleus				
external lateral	273.7 ± 20.7	**204.0 ± 18.0***	89.7 ± 4.7	**107.5 ± 3.2***
external medial	211.5 ± 23.0	**140.1 ± 8.0***	82.0 ± 14.0	89.4 ± 2.2

Data are expressed as mean ± SEM. Significant differences are indicated in **bold*** ($P < .05$ or less). Based upon Wolinsky, Carr, Hiller and Simon (73,74).

gand exposure and up-regulation to decreased ligand exposure. However, it has been shown that intermittent exposure to agonists with high intrinsic efficacy and continuous exposure to agonists with low intrinsic efficacy can both produce opioid receptor up-regulation (76). Of the sites in which binding changes were observed, habenula, basolateral amygdala, and parabrachial nucleus could all plausibly influence LHSS, inasmuch as these brain regions exert control over LHSS and/or impulse flow in the mesolimbic dopamine pathway (77–79). Given the probable relation between sensitization of brain reward and the enhanced incentive effect of food, it is noteworthy that three of the six brain regions in which binding changes occurred have strong anatomical and functional connections related to taste reactivity and/or taste aversion learning (i.e. bed nucleus of the stria terminalis, basolateral/basomedial amygdala, parabrachial nucleus) (80,81).

Brain Regional Levels of Prodynorphin-Derived Peptides. In the light of the reversal of opioid effects in stimulation-induced feeding by dynorphin A antisera, plus the involvement of κ receptors in both feeding and LHSS, effects of chronic food restriction on brain regional levels of prodynorphin-derived peptides were determined (82). As in the autoradiography study, rats had restricted access to food for two weeks and were sacrificed at mealtime on the final day. Levels of immunoreactive dynorphin A_{1-17}, dynorphin A_{1-8} and dynorphin B_{1-13} were measured in eleven brain regions known to be involved in appetite, taste and reward. Of the 33 comparisons made (i.e. 3 peptides × 11 regions), food-restricted rats displayed seven significant changes: levels of A_{1-17} increased in dorsomedial, ventromedial and medial preoptic hypothalamic areas and decreased in central amygdala; levels of A_{1-8} increased in nucleus accumbens, bed nucleus of the stria terminalis and lateral hypothalamus (Tables III and IV). The increased levels of A_{1-17} in dorsomedial and ventromedial hypothalamus and increased levels of A_{1-8} in lateral hypothalamus were also observed in streptozotocin-treated diabetic rats (83).

Table III. Regional Concentrations of ir-Dynorphin A_{1-17} (fmol/mg protein)*

Brain region	Ad libitum	Restricted
Nucleus accumbens	66.6 ± 8.7	75.0 ± 7.2
Caudate nucleus	20.5 ± 0.8	22.9 ± 1.9
Bed nucleus of stria terminalis	65.3 ± 3.9	74.9 ± 4.6
Ventral pallidum	157.9 ± 16.0	164.5 ± 8.6
Medial preoptic area	74.6 ± 4.9	136.5 ± 21.8[a]
Medial hypothalamus, dorsal	146.8 ± 6.5	175.6 ± 5.4[b]
Medial hypothalamus, ventral	177.0 ± 10.2	219.9 ± 17.0[a]
Lateral hypothalamus	104.9 ± 7.7	111.4 ± 8.3
Central nucleus of amygdala	104.7 ± 8.0	67.9 ± 9.7[b]
Ventral tegmental area	89.6 ± 10.0	89.2 ± 16.7
Parabrachial nucleus	152.4 ± 8.9	152.4 ± 6.8

*mean ± SEM
[a]$p < .05$
[b]$p < .01$ From Berman, Devi and Carr (82) with kind permission of Elsevier Science Ltd.

Brain Regional Levels of Prodynorphin mRNA. While region-specific changes in levels of particular dy-

Table IV. Regional Concentrations of ir-Dynorphin A_{1-8} (fmol/mg protein)*

Brain region	Ad libitum	Restricted
Nucleus accumbens	196.6 ± 16.5	264.4 ± 22.3[a]
Caudate nucleus	55.9 ± 3.6	64.8 ± 4.7
Bed nucleus of stria terminalis	130.3 ± 7.0	162.3 ± 6.7[b]
Ventral pallidum	656.9 ± 50.8	763.7 ± 37.3
Medial preoptic area	125.9 ± 18.3	119.4 ± 18.5
Medial hypothalamus, dorsal	142.5 ± 9.5	155.0 ± 6.7
Medial hypothalamus, ventral	135.4 ± 9.3	162.9 ± 10.6
Lateral hypothalamus	233.9 ± 23.5	332.1 ± 35.0[a]
Central nucleus of amygdala	175.8 ± 16.9	173.8 ± 11.9
Parabrachial nucleus	233.9 ± 19.1	266.8 ± 21.2

*mean ± SEM
[a]$p < .05$
[b]$p < .01$ From Berman, Devi and Carr (82) with kind permission of Elsevier Science Ltd.

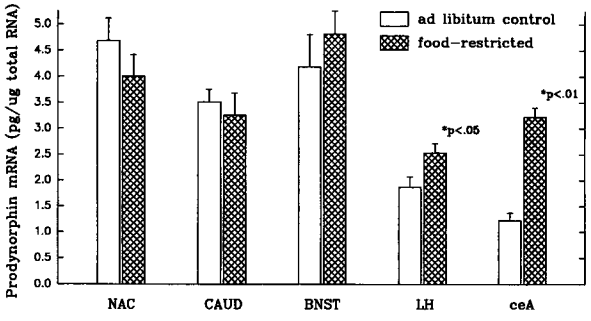

Fig. 10. Two weight-matched groups of rats were subject to either continuation of *ad libitum* feeding (n = 18) or food restriction (approximately 40% ad libitum intake) and sacrificed after two weeks. Individual brain regions were micropunched from frozen sections and picogram amounts of prodynorphin mRNA were determined in extracts using a quantitative solution hybridization assay. Mean (±SEM) levels of prodynorphin mRNA, expressed as picograms per microgram of total RNA, are displayed for nucleus accumbens (NAC), caudate nucleus (CAUD), bed nucleus of the stria terminalis (BNST), lateral hypothalamus (LH) and central amygdala (ceA). Based upon data reported by Berman, Devi, Spangler, Kreek and Carr (85).

norphin A fragments suggest altered dynorphin function during food restriction, it is not known whether they reflect changes in release, posttranslational processing or degradation. In order to shed further light on the physiological meaning of peptide levels, a quantitative solution hybridization mRNA assay was used to measure prodynorphin gene expression in a number of these same brain regions. Because gene expression is limited to cell bodies and covaries with biosynthetic demand for peptide products (84), knowledge of the mRNA levels can help elucidate the neuropeptidergic response to metabolic need. As in the previous studies, rats were sacrificed prior to mealtime on the fifteenth day of food restriction. Five brain regions, with at least medium densities of dynorphin-containing cell bodies were micropunched from frozen sections and picogram amounts of prodynorphin mRNA were determined. Food restriction significantly increased the levels of prodynorphin mRNA in the lateral hypothalamus and central amygdala, but had no effect in nucleus accumbens, caudate nucleus, or bed nucleus of the stria terminalis (85) (Fig. 10).

DISCUSSION

A Candidate Opioid Pathway. While investigations of the brain opioid system in food-restricted rats have not been exhaustive, at least one opioid pathway emerges as a possible mediator of reward sensitization; specifically, a population of LH dynorphin neurons that innervate the parabrachial nucleus (PBN). Both food restriction and diabetes increased LH levels of dynorphin A_{1-8} peptide (82,83) and prodynorphin mRNA (85), indicating increased biosynthetic demand and, presumably, increased peptide release. The LH cluster of dynorphin-containing neurons co-localizes with our stimulating electrodes, dorsal and lateral to the fornix, and innervates several opioid receptor fields (86). Among the targets of this dynorphin pathway is the PBN where food restriction increased κ and decreased μ binding (74). Involvement of an LH-PBN dynorphin pathway in reward sensitization is plausible from a functional standpoint. The PBN relays gustatory and abdominal visceral information to hypothalamic and limbic structures (87,88) and supports self-stimulation that is abolished by cytotoxic lesions of the LH (77). Not only do LH lesions block the rewarding effect of PBN stimulation, but they eliminate animals' normal preference for saccharin solutions (89). The loss of saccharin preference can be reinstated, however, by PBN microinjections of morphine (89). Thus, morphine microinjections may replace a LH dynorphinergic input that facilitates the rewarding effect of food taste. In further support of this possibility, the feeding response elicited by LH electrical stimulation, which may be mediated by the same opioid mechanism that sensitizes reward (see above), is blocked by microinjection of naloxone in the PBN (90).

The Relation Between Metabolic Need and Brain Opioid Neurons. The sites in which food restriction increased prodynorphin mRNA also happen to contain cells that are responsive to changes in energy metabolism. The LH is unique among brain regions in displaying increased uptake and utilization of free fatty acids during starvation (91,92). The dynorphinergic neurons of LH, in particular, display an immediate early gene

response to systemic insulin injections that produce cellular glucopenia and hyperphagia (93). Our failure to mimic the food restriction effect with acute glucoprivic and lipoprivic treatments suggest that transient changes in metabolic activity do not modulate reward. However, it is possible that a sustained change in LH neuronal activity leads to neuroadaptations that mediate reward sensitization. The central amygdala (ceA), which is innervated by LH dynorphin neurons (86) and displayed an even greater prodynorphin response to metabolic need, is the only forebrain structure that displays an immediate early gene response to lipoprivic treatments (94). While it is not known whether cells that respond to changes in lipid metabolism are the same as those that synthesize prodynorphin-derived peptides, ceA should similarly be considered a site in which a sustained response to metabolic need may be involved in reward sensitization.

The Opioid Response to Metabolic Need: Possible Relation to Drug Abuse. Whether the changes in brain opioid activity that accompany food-restriction and sensitize LHSS also account for the increased reinforcing efficacy of abused drugs remains to be determined. However, there is extensive evidence compatible with the hypothesis that changes in endogenous opioid activity would alter behavioral responsivity to drugs of abuse. First, it appears that all drugs of abuse exert their rewarding effects via endogenous opioid mechanisms. Activation of the brain reward system, as indexed by the lowering of self-stimulation threshold, by amphetamine, cocaine, ethanol, benzodiazepines and THC is reduced, in all cases, by naloxone or naltrexone (for review, see 95). In fact, the direct rewarding effect of cocaine, evaluated by place preference conditioning, is reduced by naloxone (96) and the δ opioid antagonist, naltrindole (97).

Brain opioid activity may also have a predisposing effect on psychostimulant and opiate self-administration inasmuch as morphine infused into the ventral tegmentum reinstates responding for intravenous cocaine and heroin following extinction (98). The inference that endogenous opioid activity would have a predisposing effect on drug taking is supported by conditioning studies in animals and clinical observations in humans. For example, the preference animals express for environments associated with cocaine and the hyperactivity they display in response to cues associated with morphine are blocked by naloxone (99,100). Both of these conditioned responses are considered to be models of drug craving and may be related to the clinically important demonstration that naltrexone attenuates craving and relapse in detoxified alcoholics (101). Underscoring, once again, the overlap between drug motivation and food motivation, naltrexone diminishes pathological binge-eating in bulimic patients (102,103).

While the effects of naloxone and naltrexone, discussed above, may be μ-receptor mediated, dynorphin peptides and the κ receptor appear to play a modulatory role in relation to μ opiate effects. Dynorphin A and synthetic κ agonists reverse the analgesic tolerance and prevent the locomotor sensitization that otherwise result from chronic morphine exposure while the κ antagonist, nor-binaltorphimine, has the opposite effect (104–107). Thus, one scenario to explain μ and κ involvement in reward sensitization would be that a tonic increase in μ receptor stimulation mediates reward sensitization while concurrent stimulation of κ receptors prevents the development of μ tolerance; blockade of either μ or κ receptors would reverse the effect. With appropriate neuroanatomical placement, such a mechanism could maintain a persistently sensitized neural substrate that would amplify the response to food taste, electrical brain stimulation and drugs of abuse.

CONCLUSION

The work reviewed in this paper suggests that one adaptive function of the brain opioid system is to sensitize organisms to the incentive-motivating effects of food as a function of metabolic need or adipose depletion. Preliminary evidence specifically indicates the involvement of μ and κ opioid receptors, possibly located in receptor fields innervated by LH and/or ceA dynorphin neurons. Insofar as drugs of abuse exert their reinforcing effects by activating the neuronal circuitry that mediates incentive-motivating effects of food, the opioid mechanism that sensitizes reward during metabolic need states may account for the increased reinforcing efficacy of abused drugs during food-restriction and contribute to the high comorbidity of eating disorders and substance abuse.

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