



# Food scarcity, neuroadaptations, and the pathogenic potential of dieting in an unnatural ecology: Binge eating and drug abuse

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## ABSTRACT

In the laboratory, food restriction has been shown to induce neuroadaptations in brain reward circuitry which are likely to be among those that facilitate survival during periods of food scarcity in the wild. However, the upregulation of mechanisms that promote foraging and reward-related learning may pose a hazard when food restriction is self-imposed in an ecology of abundant appetitive rewards. For example, episodes of loss of control during weight-loss dieting, use of drugs with addictive potential as diet aids, and alternating fasting with alcohol consumption in order to avoid weight gain, may induce synaptic plasticity that increases the risk of enduring maladaptive reward-directed behavior. In the present mini-review, representative basic research findings are outlined which indicate that food restriction alters the function of mesoaccumbens dopamine neurons, potentiates cellular and behavioral responses to D-1 and D-2 dopamine receptor stimulation, and increases stimulus-induced synaptic insertion of AMPA receptors in nucleus accumbens. Possible mechanistic underpinnings of increased drug reward magnitude, drug-seeking, and binge intake of sucrose in food-restricted animal subjects are discussed and possible implications for human weight-loss dieting are considered.

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## 1. Introduction

In recent years there has been interest in the possible therapeutic use of controlled caloric restriction to induce the physiological and behavioral adaptations which accompany food scarcity in the wild. These adaptive responses are diverse and are generally aimed at conserving energy, prolonging survival, and promoting foraging and procurement of food. Consequently, caloric restriction has been reported to reduce oxidative stress, lower the risk of cardiovascular disease, increase resistance to neurotoxins, slow cognitive decline with age, and increase lifespan in many species (e.g., [1–3]). In addition, restricted feeding has been reported to exert mood-elevating and analgesic effects in humans [4], antidepressant and anxiolytic effects in animal models [5–8], and increase incentive motivational responses in humans and rodents [9–13]. Neurophysiological correlates of the robust behavioral phenotype of the food-restricted subject were recently investigated using c-fos immunohistochemistry. Chronically food-restricted rats exposed to a nonthreatening novel environment displayed increased activation throughout a network of structures involved in antidepressant efficacy and incentive motivation, including ventral tegmental area, nucleus accumbens, and the piriform, anterior cingulate, and secondary motor cortices (Antoine, Austin, Stone and Carr, in preparation).

While controlled caloric restriction may be sustainable and beneficial when embedded within a supportive cognitive or social framework, weight-loss dieting in an ecology of abundant appetitive rewards has the potential to engender maladaptive compulsive behavior. Restrained eating often leads to loss of control, bingeing, and counterproductive weight gain [14–17], and severe dieting is a risk factor for binge pathology [18]. Moreover, associations between food restriction, binge pathology, and substance abuse have been observed in clinical populations [19,20], college students [21] and, most recently, high school students [22,23]. The deliberate pairing of food restriction and drugs of abuse is not an uncommon practice, as in the use of tobacco and psychostimulants for appetite suppression [24,25] or the increasingly popular “drunkorexia” among college-age women (i.e., fasting during the day in order to binge drink at night without weight gain) [26]. In light of the shared neural substrates of ingestive behavior and drug abuse [27–30], and the neuroadaptations induced by food restriction to be described below, the neuroplastic changes which underlie drug addiction [31] may develop in response to supranormally rewarding foods, and occur more readily in response to drugs, if subjects are repeatedly exposed during food restriction.

## 2. Early behavioral and microdialysis studies

In the mid-1980s Bart Hoebel and colleagues developed an *in vivo* microdialysis system which enabled sampling of extracellular fluid in multiple small regions of rat brain [32]. Implementing this technical advance they demonstrated that systemically administered d-amphetamine increased extracellular DA concentrations [33],

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as did an episode of feeding in food-restricted rats, and electrical stimulation delivered via lateral hypothalamic electrodes in sites that supported feeding and self-stimulation [34]. These findings not only supported the emerging concept of a shared neural substrate for rewarding effects of food and drugs, but also provided insight into the threshold-lowering effects of sweet taste [35] and drugs of abuse [36,37] on lateral hypothalamic self-stimulation. Furthermore, they offered a potential window into the well-established finding that food restriction increases the oral and intravenous self-administration of a wide variety of abused drugs [38,39]. Consequently, in 1995 Hoebel, with Pothos and Creese [40], demonstrated that rats subjected to a relatively severe food restriction regimen (20–30% loss of body weight within 7–10 days) displayed basal extracellular DA concentrations in NAc that were ~50% lower than in AL rats. Further, although the locomotor-activating effect of d-amphetamine, and intake and behavioral excitement triggered by an offered meal, were greater in FR than AL rats, the increase in NAc extracellular DA produced by d-amphetamine, morphine, and food were all blunted in FR relative to AL subjects. This set of findings raised a number of questions which were addressed in a series of studies conducted in our laboratory. In these studies, a FR protocol was used in which the daily food allotment of mature male rats was decreased to about 50% of AL intake until body weight declined by 20% (~2 weeks); from this point onward, daily feeding was titrated to clamp body weight at the new value, never exceeding 70% of the daily caloric intake of age-matched AL control subjects. Experimental testing, whether behavioral or biochemical, was initiated once body weight had stabilized at the decreased level for at least one week.

### 3. Food restriction may decrease basal dopamine activity but increases drug reward magnitude and evoked fos expression in dopamine terminal fields

To evaluate drug reward magnitude in previously drug-naïve rats, a learning-free measure was used in which subjects self-administered brief trains of reinforcing lateral hypothalamic electrical stimulation, with the available brain stimulation frequency being varied systematically over trials. In this paradigm, experimenter-administered drugs of abuse produce a leftward shift in the curve that relates rate of reinforcement to brain stimulation frequency, and the extent of this shift is taken as the measure of drug reward magnitude. An array of abused drugs, including d-amphetamine and cocaine, produced greater dose-related leftward shifts in the curves of FR relative to AL subjects whether the drugs were administered systemically, intracerebroventricularly, or directly by microinjection into NAc [41–43]. When tested in a progressive ratio protocol, in which the number of lever press responses required to obtain each 1-sec train of reinforcing brain stimulation was progressively increased over the course of each series, d-amphetamine produced a 3-fold greater increase in the amount of work FR rats performed as compared to AL rats [44]. The enhanced behavioral responsiveness of FR subjects extended to the locomotor-activating effects of drugs injected systemically, intracerebroventricularly, and directly into NAc [41,43,45], as well as to drug-free wheel-running in a protocol in which subjects had access to a wheel outside of the home cage for a 1-h period each day [46].

The findings of the Hoebel lab, indicating that both basal and stimulated DA release in NAc are diminished in FR subjects were not observed by Rouge-Pont and coworkers [47] in a protocol of mild and brief FR (body weight decreased by 10% with experiments conducted during the second week) in which there was no reported change in NAc basal extracellular DA concentration but an enhanced response to cocaine challenge. In a protocol more similar to that of the Hoebel group, Cadoni and colleagues observed that cocaine and d-amphetamine challenge produced greater elevations of extracellular DA concentration in the NAc core, but not shell, of FR subjects [48]. However, a number of findings obtained with the protocol used in our laboratory are consistent with decreased basal DA neuronal activity. For example, FR subjects

displayed decreased levels of preprodynorphin and preprotachykinin mRNA in NAc [49]; these neuropeptides are expressed in D-1 DA receptor expressing medium spiny neurons and levels are positively regulated via D-1 DA receptor signaling. FR subjects also displayed decreased NAc tyrosine hydroxylation following administration of a DOPA decarboxylase inhibitor, suggesting decreased DA synthetic activity [50]. In response to d-amphetamine challenge, FR subjects displayed decreased NAc phosphorylation of tyrosine hydroxylase on Ser40, suggesting increased feedback inhibition of DA synthesis [50]. FR subjects also displayed a significant decrease in the NAc  $V_{max}$  for DA uptake without change in the  $K_m$  [51], which is consonant with reduced surface presence of the DA transporter—a possible compensatory adaptation to decreased release. Most recently, the responsiveness of VTA DA neurons to excitatory glutamate input after FR were examined using voltage-clamp recording in midbrain slices, and displayed a 50% decrease in EPSC amplitude [52]. Yet, despite these indications of dampened DA neuronal activity during FR, cellular activation in DA terminal fields in response to a challenge dose of d-amphetamine, as determined by fos-immunostaining, paralleled the behavioral findings with greater effects in FR than AL subjects [53]. Importantly, the same result was obtained when subjects were challenged with a direct D-1 DA receptor agonist, SKF-82958 [45], suggesting that the enhanced response of FR subjects to drugs of abuse could be mediated in whole or part by an upregulation of postsynaptic receptor signaling.

Behavioral studies conducted with direct DA receptor agonists have been supportive of upregulated receptor function. D-1 DA receptor agonist administration via the systemic, intracerebroventricular, and intra-NAc routes has produced stronger locomotor responses and greater reward-potentiating effects in the LHSS protocol in FR than in AL rats [43,45,54]. Administration of the D-2/3 receptor agonist, quinpirole, via the systemic and intracerebroventricular route produced greater locomotor-activating effects in FR than in AL rats. In the LHSS protocol, quinpirole decreases the stimulation frequency threshold for initiation of lever pressing. On this measure, FR subjects displayed an enhanced response when quinpirole was administered systemically and directly into NAc [43,54]. However, given that: (1) the rewarding and cellular activating effects of D-1 DA receptor stimulation were consistently and markedly greater in FR than AL subjects, and (2) the enhanced rewarding effect of d-amphetamine microinjected in NAc was reversed by a low dose of the D-1 DA receptor antagonist SCH-23390 [43], and (3) D-1 DA receptor-linked signaling cascades are involved in the synaptic plasticity which underlies the transition from drug use to addiction [31,55], our subsequent studies of intracellular signaling and gene expression focused more narrowly on events downstream of D-1 DA receptor stimulation.

### 4. Upregulated cellular responses to D-1 DA receptor stimulation: candidate mechanisms of increased drug reward sensitivity and reward-related learning

Acute challenge with the D-1 DA receptor agonist, SKF-82958, produced greater phosphorylation of ERK 1/2 MAP kinase and the downstream nuclear transcription factor CREB, and increased preprodynorphin and preprotachykinin gene expression in NAc of FR relative to AL rats [56,57]. In addition, FR subjects displayed increased phosphorylation of the NMDA receptor NR1 subunit and CaMK II [57]. The increased activation of ERK 1/2, CaMK II and CREB were shown to be NMDA receptor-dependent in as much as they were blocked by pretreatment with the noncompetitive antagonist, MK-801. The increased activation of CREB and fos expression were also blocked by pretreatment with the ERK 1/2 MAP kinase inhibitor, SL-327 [57,58]. SL-327 did not, however, diminish the acute rewarding or locomotor-activating effects of SKF-82958 and d-amphetamine. These results support the hypothesized upregulation of NAc D-1 DA receptor function in FR rats but also suggest that key intracellular responses

may be dependent upon D-1 receptor-mediated regulation of NMDA receptor function. In addition, increased ERK 1/2 signaling and downstream effects, including CREB phosphorylation, appear unlikely to regulate the acute behavioral response to drug administration.

The increased stimulation-induced MAP kinase signaling was nevertheless of interest given the general involvement of ERK 1/2 in synaptic plasticity [59,60] and its specific involvement, within NAc, in the acquisition [61], expression and reconsolidation [62] of drug-reinforced conditioned place preference (CPP). The CPP paradigm potentially provides insight into functional components of drug responsiveness and addiction that may be of greater clinical importance than acute responsiveness to drug challenge in otherwise drug naïve subjects. CPP offers an opportunity to assess drug-reinforced associative learning, resistance to extinction, and reinstatement of an extinguished drug-seeking response. Consequently, we have recently observed that FR subjects have a lower threshold reinforcing dose, confirming findings previously reported by several labs [63–65]. FR rats are also more resistant to extinction of a cocaine-reinforced CPP, and more responsive to the reinstating effect of a priming dose of cocaine ([66]; Zheng, Cabeza de Vaca and Carr, in preparation). Further, if NAc is examined immediately after the first pairing of cocaine with a compartment of the CPP apparatus, FR subjects display greater activation of ERK 1/2 than do AL subjects. Also of interest is an increased phosphorylation of the glutamate AMPA receptor GluR1 subunit on Ser845, which was not seen in AL rats receiving cocaine, nor in FR rats receiving saline during their first conditioning session.

AMPA receptors are co-expressed with DA receptors in striatal neurons [67,68] and mediate fast excitatory synaptic transmission [69,70]. Phosphorylation of GluR1 on Ser845 by D-1 receptor-regulated cAMP or NMDA receptor-regulated cGMP pathways enhances AMPA currents and facilitates rapid insertion into the postsynapse [71–75], resulting in synaptic strengthening [70,76,77]. Thus, phosphorylation of GluR1 on Ser845 can transiently increase neuronal excitability and/or serve as the first step in a two-step process whereby cytoplasmic AMPA receptors are trafficked to the synaptic membrane as the mechanistic underpinning of experience-dependent behavioral plasticity [78]. Given our prior evidence of increased D-1 and NMDA receptor-dependent intracellular signaling in NAc of FR subjects, we challenged AL and FR rats with an acute injection of SKF-82958 and 20-min later assessed GluR1 phosphorylation in NAc [79]. Both diet groups displayed greater phosphorylation of GluR1 on Ser845, relative to vehicle-treated controls, but the response was greater in FR subjects. This result suggests that the NAc GluR1 phosphorylation seen in FR rats following their first CPP conditioning session with cocaine was a consequence of upregulated D-1 DA receptor signaling and may reflect the initial step in the synaptic plasticity underlying increased cocaine-reinforced associative learning.

### 5. Similar effects of drugs and sucrose on AMPA receptor GluR1 subunit phosphorylation

Sucrose, by way of orosensory [80,81] and postingestive [82] signaling, leads to increased extracellular DA concentrations in NAc [83,84]. Given the proposal that refined sugars, such as sucrose, generate a supranormal reward signal in brain (e.g., [85]), and their intermittent intake, alternated with periods of total food deprivation produces addiction-like behavior [86], we also tested whether brief intake of sucrose could increase NAc GluR1 phosphorylation in a manner similar to cocaine and SKF-82958. AL and FR rats were trained to drink 10% sucrose during a brief access period on 4 occasions spaced several days apart. To equalize volume ingested between diet groups (~12 ml), FR rats had access for 5-min and AL rats had access for 8-min on the final occasion, immediately after which, brains were obtained for biochemical assay. Relative to AL and FR rats that only

had access to tap water, FR rats that ingested sucrose displayed increased phosphorylation of GluR1 on Ser845 while AL rats that ingested sucrose did not. Not only does this finding represent a parallel between sucrose, cocaine, and SKF-82958, but the food restriction-dependency of the effect in all three cases could be a clue to the mechanistic basis of increased drug self-administration in FR subjects, and the importance of food restriction or deprivation in the genesis of binge eating in animal models [86–88] and human patients [18]. To test whether AMPA receptors contribute to the acute rewarding effect of D-1 DA receptor stimulation in FR subjects, SKF82958 was microinjected into NAc shell with and without 1-NA-spermine, an antagonist of Ca<sup>2+</sup>-permeable AMPA receptors. 1-NA-spermine decreased the rewarding effect of SKF82958 in FR but not AL rats, suggesting that increased AMPA receptor function contributes to the enhanced behavioral response of FR rats to acute drug challenge.

### 6. DA-mediated “overlearning” in response to palatable food and drugs during food restriction?

There is evidence that mechanisms involved in synaptic plasticity that are upregulated by FR are not exclusively postsynaptic. Specifically, FR may sustain the function of NAc shell DA release as a mediator of reward-related learning. Ventral tegmental DA neuronal burst firing has been characterized as a “teaching signal” [89], and NAc convergence of DA with glutamate-coded signals arising from hippocampus, basolateral amygdala, and medial prefrontal cortex [90,91], regulate NAc neuronal activity (e.g., [92]) and may bind rewarding events to context, cues and instrumental responses by inducing neuroplastic changes in NAc microcircuitry [31,93–95]. When rats are presented with a highly palatable food for the first time, it triggers DA release in the NAc shell [96,97]. When subjects with previous exposure to that food are presented with it again, the NAc shell DA response is blunted despite avid consumption [97,98]. If subjects have learned a maze running task required to gain access to the food, the NAc shell DA response is lost, although the food is consumed [97]. Thus, an important difference between natural reward and drugs of abuse, is that the latter retain their ability to produce a robust DA response in NAc shell with each administration [99]. Consequently, drug addiction has been proposed to be a case of “overlearning” based on repetitive activation of DA-dependent cellular responses in NAc shell which mediate synaptic plasticity and reward-related learning [31]. This overlearning would have the effect of strengthening NAc neuronal ensembles dedicated to drug-seeking and drug-taking relative to ensembles dedicated to other, natural, forms of reward-directed behavior [100]. Thus, it is of interest that when subjects are food-deprived, palatable food retains its ability to release DA in NAc shell despite the subject’s familiarity with it [98], rendering food more “drug-like” in this regard. Moreover, in the food-deprived subject this presentation of familiar palatable food retains its ability to activate intracellular signaling pathways downstream of the D-1 DA receptor, leading to phosphorylation of both the NMDA NR1 and AMPA receptor GluR1 subunits [101]. Thus, in two well developed preclinical models of binge eating disorder, repeated cycles of food restriction or deprivation combined with periodic access to highly palatable food are necessary conditions for the emergence of binge eating behavior [86–88,102]. In the model developed in the Hoebel laboratory [103,104], it proved essential that 12-h periods of access to chow plus sucrose be alternated with 12-h periods of total food deprivation in order for binge-like intake of sucrose to develop over days; full-time access to chow and sucrose did not lead to bingeing. Relating this phenomenon back to NAc DA release as a teaching signal, Hoebel with Avena and Rada demonstrated that in their sucrose-binge eating protocol, sucrose retained its ability to release DA in NAc shell. Moreover, if subjects were chronically food-restricted on the chow component of their diet such that body weight declined by 15%, the DA response to sucrose during the sucrose-binge protocol was further

increased [105]. Thus, it seems likely that for sucrose and drugs of abuse, a sustained ability to release DA in NAc shell, in conjunction with postsynaptic neuroadaptations, increases synaptic plasticity and strengthens the corresponding reward-directed behavior.

### 7. Synaptic insertion of AMPA receptors: a new focus in the exploration of acute and enduring effects of food restriction on reward-directed behavior

It was recently observed that brief intake of sucrose by AL rats increased GluR1 abundance in the NAc postsynaptic density—a finding indicated by subcellular fractionation and Western analysis, and then confirmed by electron microscopy (Tukey, Ferreira, Antoine, Ninan, Cabeza de Vaca, Hartner, Goffer, Guarini, Marzan, Mahajan, Carr, Aoki, and Ziff, under review). In a follow-up study, we investigated whether brief intake of sucrose during FR increases trafficking of AMPA receptors to the synaptic membrane in NAc [106]. Using a subcellular fractionation method it was determined that neither FR nor sucrose altered levels of GluR1 or GluR2 protein in the NAc whole cell preparation, suggesting no alteration in synthesis or degradation of these AMPAR subunits. However, in AL subjects, sucrose intake produced a modest but significant increase in GluR1, but not GluR2, abundance in the postsynaptic density fraction, which could be reflective of increased trafficking of GluR1 homomers or GluR1/GluR2 heteromers, both of which are relatively rare in NAc, but are Ca<sup>2+</sup>-permeable and increase neuronal excitability. In FR subjects, sucrose intake produced a pronounced increase in both GluR1 and GluR2 in the NAc postsynaptic density. Given that the majority of GluR1 in NAc is physically associated with GluR2 and most GluR2 that is not associated with GluR1 appears to represent partially assembled receptors [107], the most parsimonious interpretation of this finding is that sucrose intake during FR increased insertion of GluR1/GluR2 heteromers.

GluR1/GluR2 heteromers are trafficked to the synapse in an activity-dependent manner and mediate synaptic strengthening [70,108,109] and associative learning [109]. In cell culture, activity-dependent trafficking of GluR1/GluR2 heteromers has been shown to rapidly follow D-1 DA receptor stimulation and display NMDA and AMPA receptor-dependence [110]. This suggests a plausible connection between our findings of upregulated D-1 receptor signaling, consequent increases in phosphorylation of NMDA and AMPA receptor subunits, and the sucrose-induced insertion of GluR1-containing AMPA receptors in the NAc postsynaptic density of FR rats. Speculatively, sucrose-induced trafficking of AMPA receptors to the NAc postsynaptic density could be a key to the synaptic plasticity that underlies enduring changes in sucrose-directed behavior, including the disposition to binge. The plausibility of this speculation gains support from findings that withdrawal from chronic cocaine is associated with increased AMPA receptor surface expression in NAc [111,112], and the persistent craving and vulnerability to relapse in withdrawn subjects is dependent on glutamate release and AMPA receptors [112–114].

### 8. Concluding comment

The parallel between compulsive use of food and drugs has become a topic of interest and productive research [30,115]. Among the risk factors that may increase vulnerability to both are food restriction and the concomitant neuroadaptations which evolved to enable survival through alternating cycles of food scarcity and abundance. Weight-loss dieting amidst an abundance of supranormally rewarding foods and cues signaling their availability is likely to be stressful and inevitably lead to episodes of loss of control. Such episodes may be hazardous based on their enhanced capacity to induce neuroplastic changes, ingraining the corresponding behavior and, perhaps, contributing to the genesis of binge pathology. Unlike

food, drugs of abuse may not readily or necessarily be encountered by many individuals. Nevertheless, understanding modulatory effects of diet and body weight on functional components of the drug abuse and addiction process has potential to illuminate risk factors, preventatives and interventions. Moreover, there are the concrete instances in which food restriction and drug use are coupled, as in the use of stimulants to suppress appetite and the anorexia that is secondary to drug abuse, where understanding the nature and mechanisms of interaction may have implications for prevention and treatment. Results outlined above provide some examples of the beneficial cross-talk between behavioral neuroscience subfields focusing on drug addiction and ingestive behavior, and are consonant with the current concept that diverse forms of compulsive reward-directed behavior are rooted in common underlying CNS mechanisms, and that their decompartmentalization may facilitate research and development of crossover therapies [116].

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### References

- [1] Ingram DK, Zhu M, Mamczarz J, Zou S, Lane MA, Roth GS, et al. Calorie restriction mimetics: an emerging research field. *Aging Cell* 2006;5:97–108.
- [2] Mattson MP. Dietary factors, hormesis and health. *Ageing Res Rev* 2008;7:43–8.
- [3] Canto C, Auwerx J. Caloric restriction, SIRT1 and longevity. *Trends Endocrinol Metab* 2009;20:325–31.
- [4] Michalsen A. Prolonged fasting as a method of mood enhancement in chronic pain syndromes: a review of clinical evidence and mechanisms. *Curr Pain Headache Rep* 2010;14:80–7.
- [5] Inoue K, Zorrilla EP, Tabarin A, Valdez GR, Iwasaki S, Kiriike N, et al. Reduction of anxiety after restricted feeding in the rat: implication for eating disorders. *Biol Psychiat* 2004;55:1075–81.
- [6] Levay EA, Govic A, Penman J, Paolini AG, Kent S. Effects of adult-onset calorie restriction on anxiety-like behavior in rats. *Physiol Behav* 2007;92:889–96.
- [7] Lutter M, Krishnan V, Russo SJ, Jung S, McClung CA, Nestler EJ. Orexin signaling mediates the antidepressant-like effect of calorie restriction. *J Neurosci* 2008;28:3071–5.
- [8] Yamamoto Y, Tanahashi T, Kawai T, Chikahisa S, Katsuura S, Nishida K, et al. Changes in behavior and gene expression induced by caloric restriction in C57BL/6 mice. *Physiol Genomics* 2009;39:227–35.
- [9] Jansen A, van den Hout M. On being led into temptation: “counterregulation” of dieters after smelling a “preload”. *Addictive Behav* 1991;16:247–53.
- [10] Carr KD, Wolinsky TD. Chronic food restriction and weight loss produce opioid facilitation of perifornical hypothalamic self-stimulation. *Brain Res* 1993;607:141–8.
- [11] Fedoroff IC, Polivy J, Herman CP. The effect of pre-exposure to food cues on the eating behavior of restrained and unrestrained eaters. *Appetite* 1997;28:33–47.
- [12] Fedoroff IC, Polivy J, Herman CP. The specificity of restrained versus unrestrained eaters' responses to food cues: general desire to eat, or craving for the cued food? *Appetite* 2003;41:7–13.
- [13] Fulton S, Woodside B, Shizgal P. Modulation of brain reward circuitry by leptin. *Science* 2000;287:125–8.
- [14] Vitousek KM. The case for semi-starvation. *Eur Eat Disord Rev* 2004;12:275–8.
- [15] Vitousek KM, Gray JA, Grubbs KM. Caloric restriction for longevity: I. Paradigm, protocols and physiological findings in animal research. *Eur Eat Disord Rev* 2004;12:279–99.
- [16] Polivy J, Herman PC. An evolutionary perspective on dieting. *Appetite* 2006;47:30–5.
- [17] Polivy J, Herman PC, Coelho JS. Caloric restriction in the presence of attractive food cues: external cues, eating, and weight. *Physiol Behav* 2008;94:729–33.
- [18] Stice E, Davis K, Miller NP, Marti NC. Fasting increases risk for onset of binge eating and bulimic pathology: a 5-year prospective study. *J Abnorm Psychol* 2008;117:941–6.
- [19] Krahn D, Kurth C, Demitrack M, Drewnowski A. The relationship of dieting severity and bulimic behaviors to alcohol and other drug use in young women. *J Subst Abuse* 1992;4:341–53.
- [20] Wiederman MW, Pryor T. Substance abuse and impulsive behaviors among adolescents with eating disorders. *Addictive Behav* 1996;21:269–72.
- [21] Krahn DD, Kurth CL, Gombert E, Drewnowski A. Pathological dieting and alcohol use in college women—a continuum of behaviors. *Eat Behav* 2005;6:43–52.
- [22] Pisetsky EM, Chao YM, Dierker LC, May AM, Striegel-Moore RH. Disordered eating and substance use in high-school students: results from the youth risk behavior surveillance system. *Int J Eat Disord* 2008;41:464–70.
- [23] Seo D-C, Jiang N. Associations between smoking and severe dieting among adolescents. *J Youth Adolesc* 2009;38:1364–73.

- [24] Klesges RC, Elliott VE, Robinson LA. Chronic dieting and the belief that smoking controls body weight in a biracial, population-based adolescent sample. *Tobacc Control* 1997;6:89–94.
- [25] Cochran C, Malcolm R, Brewerton T. The role of weight control as a motivation for cocaine abuse. *Addict Behav* 1998;23:201–7.
- [26] Kershaw S. Starving themselves: cocktail in hand. *NY Times*; March 2, 2008.
- [27] Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. *J Neurosci* 2002;22:3306–11.
- [28] Cardinal RN, Everitt BJ. Neural and psychological mechanisms underlying appetitive learning: links to drug addiction. *Curr Opin Neurobiol* 2004;14:156–62.
- [29] Di Chiara G. Dopamine in disturbances of food and drug motivated behavior: a case of homology? *Physiol Behav* 2005;86:9–10.
- [30] Volkow ND, Wang G-J, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Phil Trans Royal Soc Brit* 2008;363:3191–200.
- [31] Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Ann Rev Neurosci* 2006;29:565–98.
- [32] Hernandez L, Stanley BG, Hoebel BG. A small, removable microdialysis probe. *Life Sci* 1986;39:2629–37.
- [33] Hernandez L, Lee F, Hoebel BG. Simultaneous microdialysis and amphetamine infusion in the nucleus accumbens and striatum of freely moving rats: increase in extracellular dopamine and serotonin. *Brain Res Bull* 1987;19:623–8.
- [34] Hernandez L, Hoebel BG. Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. *Physiol Behav* 1988;44:599–606.
- [35] Coons EE, White HA. Tonic properties of orosensation and the modulation of intracranial self-stimulation: the CNS weighting of external and internal factors governing reward. *Ann NY Acad Sci* 1977;290:158–79.
- [36] Kornetsky C, Esposito RU, McLean S, Jacobson JO. Intracranial self-stimulation thresholds: a model for the hedonic effects of drugs of abuse. *Arch Gen Psychiat* 1979;36:289–92.
- [37] Bozarth MA, Gerber GJ, Wise RA. Intracranial self-stimulation as a technique to study the reward properties of drugs of abuse. *Pharmacol Biochem Behav* 1980;13(Suppl 1):245–7.
- [38] Carroll ME, France CP, Meisch RA. Food deprivation increases oral and intravenous drug intake in rats. *Science* 1979;205:319–21.
- [39] Carroll ME, Meisch RA. Increased drug-reinforced behavior due to food deprivation. *Adv Behav Pharmacol* 1984;4:47–88.
- [40] Pothos EN, Creese I, Hoebel BG. Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus accumbens and alters dopamine response to amphetamine, morphine, and food intake. *J Neurosci* 1995;15:6640–50.
- [41] Cabeza de Vaca S, Carr KD. Food restriction enhances the central rewarding effect of abused drugs. *J Neurosci* 1998;18:7502–10.
- [42] Carr KD, Kim G-Y, Cabeza de Vaca S. Chronic food restriction augments the central rewarding effect of cocaine and the  $\delta$ -1 opioid agonist, DPPE, but not the  $\delta$ -2 agonist, deltorphin-II. *Psychopharmacol* 2000;152:200–7.
- [43] Carr KD, Cabeza de Vaca S, Sun Y, Chau LS. Reward-potentiating effects of D-1 dopamine receptor agonist and AMPAR GluR1 antagonist in nucleus accumbens shell and their modulation by food restriction. *Psychopharmacol* 2009;202:731–43.
- [44] Cabeza de Vaca S, Krahn L, Carr KD. A progressive ratio schedule of self-stimulation testing reveals profound augmentation of d-amphetamine reward by food restriction but no effect of a "sensitizing" regimen of d-amphetamine. *Psychopharmacol* 2004;175:106–13.
- [45] Carr KD, Tsimberg Y, Berman Y, Yamamoto N. Evidence of increased dopamine receptor signaling in food-restricted rats. *Neurosci* 2003;119:1157–67.
- [46] Cabeza de Vaca S, Kannan P, Pan Y, Jiang N, Sun Y, Carr KD. The adenosine  $A_{2A}$  receptor agonist, CGS-21680, blocks excessive rearing, acquisition of wheel running, and increases nucleus accumbens CREB phosphorylation in chronically food-restricted rats. *Brain Res* 2007;1142:100–9.
- [47] Rouge-Pont F, Marinelli M, Le Moal M, Simon H, Piazza PV. Stress-induced sensitization and glucocorticoids. II. Sensitization of the increase in extracellular dopamine induced by cocaine depends on stress-induced corticosterone secretion. *J Neurosci* 1995;15:7189–95.
- [48] Cadoni C, Solinas M, Valentini V, Di Chiara G. Selective psychostimulant sensitization by food restriction: differential changes in accumbens shell and core dopamine. *Eur J Neurosci* 2003;18:2326–34.
- [49] Haberny SL, Carr KD. Comparison of basal and D-1 dopamine receptor agonist-stimulated neuropeptide gene expression in caudate-putamen and nucleus accumbens of ad libitum fed and food-restricted rats. *Molec Brain Res* 2005;141:121–7.
- [50] Pan Y, Berman Y, Haberny LY, Meller E, Carr KD. Synthesis, protein levels and phosphorylation state of tyrosine hydroxylase in mesoaccumbens and nigrostriatal dopamine pathways of chronically food-restricted rats. *Brain Res* 2006;1122:135–42.
- [51] Zhen J, Reith MEA, Carr KD. Chronic food restriction and dopamine transporter function in rat striatum. *Brain Res* 2006;1082:98–101.
- [52] Pan Y, Chau L, Liu S, Avshalumov M, Rice M, Carr KD. A food restriction protocol that increases drug reward decreases *TrkB* in the ventral tegmental area, with no effect on *BDNF* or *TrkB* protein levels in dopaminergic forebrain regions. Submitted for publication.
- [53] Carr KD, Kutchukhidze N. Chronic food restriction increases fos-like immunoreactivity induced in rat forebrain by intraventricular amphetamine. *Brain Res* 2000;861:88–96.
- [54] Carr KD, Kim G-Y, Cabeza de Vaca S. Rewarding and locomotor-activating effects of direct dopamine receptor agonists are augmented by chronic food restriction in rats. *Psychopharmacol* 2001;154:420–8.
- [55] Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacol Rev* 2008;33:166–80.
- [56] Haberny S, Berman Y, Meller E, Carr KD. Chronic food restriction increases D-1 dopamine receptor agonist-induced ERK1/2 MAP Kinase and CREB phosphorylation in caudate-putamen and nucleus accumbens. *Neurosci* 2004;125:289–98.
- [57] Haberny SL, Carr KD. Food restriction increases NMDA receptor-mediated CaMK II and NMDA receptor/ERK 1/2-mediated CREB phosphorylation in nucleus accumbens upon D-1 dopamine receptor stimulation in rats. *Neurosci* 2005;132:1035–43.
- [58] Carr KD, Cabeza de Vaca S, Sun Y, Chau LS, Pan Y, Dela Cruz J. Effects of the MEK inhibitor, SL-327, on rewarding, motor- and cellular-activating effects of D-amphetamine and SKF-82958, and their augmentation by food restriction in rat. *Psychopharmacol* 2009;201:495–506.
- [59] Sweatt JD. The neuronal MAP kinase cascade: a biochemical signal integration system subserving synaptic plasticity and memory. *J Neurochem* 2001;76:1–10.
- [60] Thomas GM, Huganir RL. MAPK cascade signaling and synaptic plasticity. *Nature Rev Neurosci* 2004;5:173–83.
- [61] Gerdjikov TV, Ross GM, Beninger RJ. Place preference induced by nucleus accumbens amphetamine is impaired by antagonists of ERK or p38 MAP kinases in rats. *Behav Neurosci* 2004;118:740–50.
- [62] Miller CA, Marshall JF. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. *Neuron* 2005;47:873–84.
- [63] Bell SM, Stewart RB, Thompson SC, Meisch RA. Food-deprivation increases cocaine-induced conditioned place preference and locomotor activity in rats. *Psychopharmacol* 1997;131:1–8.
- [64] Cabib S, Orsini C, Le Moal M, Piazza PV. Abolition and reversal of strain differences in behavioral responses to drugs of abuse after a brief experience. *Science* 2000;289:463–5.
- [65] Stuber GD, Evans SB, Higgins MS, Pu Y, Figlewicz DP. Food restriction modulates amphetamine-conditioned place preference and nucleus accumbens dopamine release in the rat. *Synapse* 2002;46:83–90.
- [66] Liu S, Zheng D, Peng X-X, Cabeza de Vaca S, Carr KD. *Enhanced cocaine-reinforced conditioned place preference and associated brain regional levels of BDNF, p-ERK1/2 and p-Ser845-GluR1 in food-restricted rats*. Submitted for publication.
- [67] Bernard V, Somogyi P, Bolam JP. Cellular, subcellular, and subsynaptic distribution of AMPA-type glutamate receptor subunits in the neostriatum of the rat. *J Neurosci* 1997;17:819–33.
- [68] Glass MJ, Lane DA, Colago EEO, Chan J, Schlussman SD, Zhou Y, et al. Chronic administration of morphine is associated with a decrease in surface AMPA GluR1 receptor subunit and dopamine D1 receptor expressing neurons in the shell and non-D1 receptor expressing neurons in the core of the rat nucleus accumbens. *Exp Neurol* 2008;210:750–61.
- [69] Hollmann M, Heinemann S. Cloned glutamate receptors. *Ann Rev Neurosci* 1994;17:31–108.
- [70] Barry MR, Ziff EB. Receptor trafficking and the plasticity of excitatory synapses. *Curr Opin Neurobiol* 2002;12:279–86.
- [71] Roche KW, O'Brien RJ, Mammen AL, Bernhardt J, Huganir RL. Characterization of multiple phosphorylation sites on the AMPA receptor GluR1 subunit. *Neuron* 1996;16:1179–88.
- [72] Snyder GL, Allen PB, Fienberg A, Valee CG, Huganir RL, Nairn AC, et al. Regulation of phosphorylation of the GluR1 AMPA receptor in the neostriatum by dopamine and psychostimulants in vivo. *J Neurosci* 2000;20:4480–8.
- [73] Banke TG, Bowie D, Lee H, Huganir RL, Schousboe A, Traynelis SF. Control of GluR1 AMPA receptor function by cAMP-dependent protein kinase. *J Neurosci* 2000;20:89–102.
- [74] Man HY, Sekine-Aizawa Y, Huganir RL. Regulation of (alpha)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor trafficking through PKA phosphorylation of the Glu receptor 1 subunit. *Proc Natl Acad Sci* 2007;104:3579–84.
- [75] Serulle Y, Zhang S, Ninan I, Puzzo D, McCarthy M, Khatri L, et al. A novel GluR1-cGKI interaction regulates AMPA receptor trafficking. *Neuron* 2007;56:270–88.
- [76] Shi S, Hayashi Y, Esteban JA, Malinow R. Subunit-specific rules governing AMPA receptor trafficking to synapses in hippocampal pyramidal neurons. *Cell* 2001;105:331–43.
- [77] Derkach VA, Oh MO, Guire ES, Soderling TR. Regulatory mechanisms of AMPA receptors in synaptic plasticity. *Nature Rev Neurosci* 2007;8:101–13.
- [78] Kessels HW, Malinow R. Synaptic AMPA receptor plasticity and behavior. *Neuron* 2009;61:340–50.
- [79] Carr KD, Chau LS, Cabeza de Vaca S, Gustafson K, Stouffer M, Tukey D, et al. AMPA receptor subunit GluR1 downstream of D-1 dopamine receptor stimulation in nucleus accumbens shell mediates increased drug reward magnitude in food-restricted rats. *Neurosci* 2010;165:1074–86.
- [80] Smith GP. Accumbens dopamine mediates the rewarding effect of orosensory stimulation by sucrose. *Appetite* 2004;43:11–3.
- [81] Yu WZ, Silva RM, Sclafani A, Delamater AR, Bodnar RJ. Role of D(1) and D(2) dopamine receptors in the acquisition and expression of flavor-preference conditioning in sham-feeding rats. *Pharmacol Biochem Behav* 2000;67:537–44.
- [82] de Araujo IE, Oliveira-Maia AJ, Sotnikova TD, Gainetdinov RR, Caron MG, Nicolelis MA, et al. Food reward in the absence of taste receptor signaling. *Neuron* 2008;57:930–41.
- [83] Hajnal A, Smith GP, Norgren R. Oral sucrose stimulation increases accumbens dopamine in the rat. *Am J Physiol Reg Integr Comp Physiol* 2004;286:R31–7.
- [84] Norgren R, Hajnal A, Mungarnde SS. Gustatory reward and the nucleus accumbens. *Physiol Behav* 2006;89:531–5.
- [85] Lenoir M, Serre F, Cantin L, Ahmed SH. Intense sweetness surpasses cocaine reward. *PLoS One* 2007;8:1–10.

- [86] Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake. *Neurosci Biobehav Rev* 2008;32:20–39.
- [87] Hagan MM, Moss DE. Persistence of binge-eating patterns after a history of restriction with intermittent bouts of refeeding on palatable food in rats: implications for bulimia nervosa. *Int J Eat Dis* 1997;22:411–20.
- [88] Hagan MM, Chandler PC, Wauford PK, Rybak RJ, Oswald KD. The role of palatable food and hunger as trigger factors in an animal model of stress induced binge eating. *Int J Eat Dis* 2003;34:198–9.
- [89] Schultz W. Predictive reward signal of dopamine neurons. *J Neurophysiol* 1998;80:1–27.
- [90] Groenewegen HJ, Wright CI, Beijer AV, Voorn P. Convergence and segregation of ventral striatal inputs and outputs. *Ann NY Acad Sci* 1999;877:49–63.
- [91] Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron* 2005;45:647–50.
- [92] Surmeier J, Ding J, Day M, Wang Z, Shen W. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. *Trends Neurosci* 2007;30:228–35.
- [93] Kelley AE. Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. *Neurosci Biobehav Rev* 2004;27:765–76.
- [94] Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. *Neuron* 2004;44:5–21.
- [95] Dalley JW, Laane K, Theobald DEH, Armstrong HC, Corlett PR, Chudasama Y, et al. Time-limited modulation of appetitive Pavlovian memory by D1 and NMDA receptors in the nucleus accumbens. *Proc Natl Acad Sci USA* 2005;102:6189–94.
- [96] Bassareo V, Di Chiara G. Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. *Neurosci* 1999;89:637–41.
- [97] Gambarana C, Masi F, Leggio B, Grappi S, Nanni G, Scheggi S, et al. Acquisition of a palatable-food-sustained appetitive behavior in satiated rats is dependent on the dopaminergic response to this food in limbic areas. *Neurosci* 2003;121:179–87.
- [98] Bassareo V, Di Chiara G. Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. *Eur J Neurosci* 1999;11:4389–97.
- [99] Pontieri FE, Tanda G, Di Chiara G. Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the “shell” as compared with the “core” of the rat nucleus accumbens. *Proc Natl Acad Sci USA* 1995;92:12304–8.
- [100] Pennartz CM, Groenewegen HJ, Lopes da Silva FH. The nucleus accumbens as a complex of functionally distinct neuronal ensembles: an integration of behavioural, electrophysiological and anatomical data. *Prog Neurobiol* 1994;42:719–61.
- [101] Danielli B, Scheggi S, Grappi S, Marchese G, Graziella De Montis M, Tagliamonte A, et al. Modifications in DARPP-32 phosphorylation pattern after repeated palatable food consumption undergo rapid habituation in the nucleus accumbens shell of non-food-deprived rats. *J Neurochem* 2010;112:531–41.
- [102] Hagan MM, Wauford PK, Chandler PC, Jarrett LA, Rybak RJ, Blackburn K. A new animal model of binge eating: key synergistic role of past caloric restriction and stress. *Physiol Behav* 2002;77:45–54.
- [103] Avena NM, Hoebel BG. A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine. *Neurosci* 2003;122:17–20.
- [104] Avena NM, Rada P, Hoebel BG. Sugar bingeing in rats. *Curr Protoc Neurosci* 2006 Chapter 9:Unit9.23C:9.23C.1–6.
- [105] Avena NM, Rada P, Hoebel BG. Underweight rats have enhanced dopamine release and blunted acetylcholine response in the nucleus accumbens while bingeing in sucrose. *Neurosci* 2008;156:865–71.
- [106] Peng X-X, Ziff EB, Carr KD. *Effects of food restriction and sucrose intake on synaptic delivery of AMPA receptors in nucleus accumbens*, *Synapse* 2011 Mar 21, doi: 10.1002/syn.20931 [Electronic publication ahead of print].
- [107] Reimers JM, Milovanovic M, Wolf ME. Quantitative analysis of AMPA receptor subunit composition in addiction-related brain regions. *Brain Res* 2011;1367:223–33.
- [108] Malinow R. AMPA receptor trafficking and long-term potentiation. *Philos Trans R Soc Lond B Biol Sci* 2003;358:707–14.
- [109] Whitlock JR, Heynen AJ, Shuler MG, Bear MF. Learning induces long-term potentiation in the hippocampus. *Science* 2006;313:1093–7.
- [110] Gao C, Wolf ME. Dopamine alters AMPA receptor synaptic expression and subunit composition in dopamine neurons of the ventral tegmental area cultured with prefrontal cortex neurons. *J Neurosci* 2007;27:14275–85.
- [111] Boudreau AC, Wolf ME. Behavioral sensitization to cocaine associated with increased AMPA receptor surface expression in the nucleus accumbens. *J Neurosci* 2005;25:9144–51.
- [112] Conrad KL, Tseng KY, Uejima JL, Reimers JM, Heng L-J, Shaham Y, et al. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature* 2008;454:118–21.
- [113] Famous KR, Kumaresan V, Sadri-Vakili G, Schmidt HD, Mierke DF, Cha JH, et al. Phosphorylation-dependent trafficking of GluR2-containing AMPA receptors in the nucleus accumbens plays a critical role in the reinstatement of cocaine seeking. *J Neurosci* 2008;28:11061–70.
- [114] Knackstedt LA, Kalivas PW. Glutamate and reinstatement. *Curr Opin Pharmacol* 2009;9:59–64.
- [115] Corwin RL, Grigson PS. Symposium overview—food addiction: fact or fiction? *J Nutr* 2009;139:617–9.
- [116] Frascella J, Potenza MN, Brown LL, Childress AR. Shared brain vulnerabilities open the way for nonsubstance addictions: carving addiction at a new joint? *Ann NY Acad Sci* 2010;1187:294–315.