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

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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 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, binging, 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],
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 Greese [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 hydroxylase 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 Vmax for DA uptake without change in the Km [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 responsiveness 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, the 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 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

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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-refrained 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-refrained 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-refrained CPP, and more responsive to the reinstating effect of a priming dose of cocaine (166; Zheng, Cabeza de Vacca 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 [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-refrained associative learning.

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

Sucrose, by way of orosensory [80,81] and postigestive [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 Ca2+-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 microcircuity [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 [98]. Subject 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 binging. 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/GluR3 heteromers, both of which are relatively rare in NAc, but are Ca2+-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 GluK1-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 superabundantly 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, preventative 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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