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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, 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],

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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

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