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# Modulatory Effects of Food Restriction on Brain and Behavioral Effects of Abused Drugs

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## Abstract

Energy homeostasis is achieved, in part, by metabolic signals that regulate the incentive motivating effects of food and its cues, thereby driving or curtailing procurement and consumption. The neural underpinnings of these regulated incentive effects have been identified as elements within the mesolimbic dopamine pathway. A separate line of research has shown that most drugs with abuse liability increase dopamine transmission in this same pathway and thereby reinforce self-administration. Consequently, one might expect shifts in energy balance and metabolic signaling to impact drug abuse risk. Basic science studies have yielded numerous examples of drug responses altered by diet manipulation. Considering the prevalence of weight loss dieting in Western societies, and the anorexigenic effects of many abused drugs themselves, we have focused on the CNS and behavioral effects of food restriction in rats. Food restriction has been shown to increase the reward magnitude of diverse drugs of abuse, and these effects have been attributed to neuroadaptations in the dopamine-innervated nucleus accumbens. The changes induced by food restriction include synaptic incorporation of calcium-permeable AMPA receptors and increased signaling downstream of D1 dopamine receptor stimulation. Recent studies suggest a mechanistic model in which concurrent stimulation of D1 and GluA2-lacking AMPA receptors enables increased stimulus-induced trafficking of GluA1/GluA2 AMPARs into the postsynaptic density, thereby increasing the incentive effects of food, drugs, and associated cues. In addition, the established role of AMPA receptor trafficking in enduring synaptic plasticity prompts speculation that drug use during food restriction may more strongly ingrain behavior relative to similar use under free-feeding conditions.

### Keywords

Reward; nucleus accumbens; food restriction; AMPA receptors; dopamine; addiction

## 1. INTRODUCTION

The abuse liability of many drugs that pose a public health threat is based on their ability to activate and potentially take control of neurocircuits that mediate the incentive-motivating and positive reinforcing effects of natural rewards. This relationship has been

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particularly well demonstrated in relation to feeding behavior. Among the findings, pointing to a common neural substrate for feeding and drug abuse, are those demonstrating that avidity for sweet taste predicts avidity for psychostimulant drugs [1,2], behavioral cross-sensitization occurs between sugar and psychostimulants [3,4], responsiveness to cocaine is elevated in rats prone to becoming obese on “junk food” [5], food restriction and obesity modulate drug-directed behavior in opposite directions [6,7], high-energy diet and chronic drug use induce overlapping neuroadaptations [8–12], and insights into behavioral and mechanistic underpinnings of drug addiction have been used to develop a hypothesis of “food addiction” [13]. Given this close association, discoveries of the endocrine adiposity hormone, leptin, and a long list of feeding-related neuropeptides have led to parallel lines of research focused on their involvement in both ingestive behavior and drug abuse [*e.g.*, 14–18]. Though these lines of research are ongoing, many examples of co-regulation have already been demonstrated.

The relationship between the physiology of energy balance and drug reward is not only of interest with regard to understanding the neurobiological basis of drug abuse, but also a variety of clinical problems. These include the high comorbidity of eating disorders and substance abuse [19–22], weight loss dieting as a risk factor for the development of binge pathology, increased drug relapse risk in individuals engaged in weight loss dieting [23,24], and increased drug-induced psychopathology among low body weight individuals [25]. Consequently, our laboratory has investigated the behavioral expression and mechanistic underpinnings of increased drug reward magnitude in chronically food-restricted rats.

## 2. EARLY BEHAVIORAL AND PHARMACOLOGICAL FINDINGS

Some of the earliest research to portend a close functional relationship between feeding behavior and drug abuse arose from the use of electrical brain stimulation in rodent models of appetitive motivation and reward. Lateral hypothalamic electrical stimulation was shown to elicit vigorous feeding behavior and, at higher stimulation frequencies, self-administration in the absence of food [26]. An indication that brain stimulation activated incentive motivation was provided by studies demonstrating a trade-off between sucrose concentration and brain stimulation frequency in rats that self-administered brief trains of stimulation only if they had the opportunity to eat during each train [27]. As the available sucrose concentration was decreased, the brain stimulation frequency needed to reinforce self-administration and concurrent consumption increased correspondingly, as if the brain stimulation was conferring incentive value that was not intrinsic to the food. Moreover, when sucrose was withdrawn altogether, a further increase in brain stimulation frequency, just above that needed to reinforce feeding for the lowest sucrose concentration, sustained self-administration for its own positive reinforcing effects (*i.e.*, intracranial self-stimulation or ICSS). Interestingly, about a decade later, it was shown that just as sucrose consumption could lower the threshold for ICSS, so could passive administration of a variety of abused drugs [28,29]. These findings indicated that sugar and abused drugs similarly combine with brain stimulation to yield a net rewarding effect that reinforces instrumental responding. In addition, just as the trade-off between sucrose concentration and brain stimulation frequency could be used to infer changes in the reward magnitude of sucrose as a function of

concentration, the trade-off between drug dose and brain stimulation frequency was adopted as a learning-free method of measuring drug reward magnitude [30].

Neurochemically, the common denominator cutting across the rewarding effects of sucrose, brain stimulation, and drugs of abuse was shown to be dopamine; particularly dopamine signaling in the nucleus accumbens. *In vivo* microdialysis studies revealed that orosensory stimulation with sucrose [31], post-oral nutritive sugar signaling [32], direct electrical stimulation of lateral hypothalamus [33], and administration of most drugs of abuse [34] increase extracellular dopamine concentration in nucleus accumbens. Moreover, blockade of local dopamine transmission through reversible dopamine receptor antagonism or irreversible neurotoxic depletion of dopamine, using 6-OHDA, decreased or eliminated instrumental responding for food [35], lateral hypothalamic electrical stimulation [36], and drugs of abuse [37, 38].

Using these same experimental methods, it was demonstrated that just as food deprivation increases the hedonic response and incentive motivating effects of food (*i.e.*, positive alliesthesia), food deprivation increases the reward magnitude of abused drugs assayed in the electrical brain stimulation reward protocol [6]. Furthermore, these effects were attributed to adaptive changes in a neural substrate as opposed to diet-related changes in pharmacokinetics or drug metabolism because they occurred regardless of whether drugs were administered systemically or directly into the brain ventricular system. A further important finding was that an acute period of total food deprivation (*e.g.*, 24 h) was not sufficient to increase drug reward magnitude; rather, a regimen of chronic food restriction leading to a maintained 20% decrease in body weight reliably produced the effect. These results provided a functional explanation for observations that food deprivation increased drug self-administration in animal models, with the maintenance of a substantially reduced body weight being necessary for the effect, as opposed to an acute withholding of food [39,40].

## 3. ON THE ROLES OF METABOLIC SIGNALING AND STRESS

In contrast to earlier formulations that posited a hard distinction between homeostatic and hedonic feeding, and the underlying hypothalamic and mesolimbic mechanisms, the discoveries of feeding-related neuropeptides and endocrine adiposity hormones with receptor populations in both the hypothalamus and mesolimbic pathway pointed to potential mechanistic bases for the regulation of incentive motivation as a fundamental feature of homeostatic behavior [*e.g.*, 41,42]. A close functional relationship between hypothalamic homeostatic mechanisms and mesolimbic reward mechanisms might have been expected based on the long-known phenomenon of positive alliesthesia [43]. Thus, the presence of receptors for leptin, insulin, ghrelin, orexin, GLP-1 and other metabolic signaling peptides in ventral tegmental area or nucleus accumbens pointed to specific candidate mediators of the link between energy balance and drug abuse risk. Each of these has gained some experimental attention aimed at assessing involvement in drug abuse though, as detailed in recent reviews, the evidence obtained to date tends to be limited or inconsistent [44–48]. An exception may be where alcohol consumption is concerned; a substantial body of evidence has implicated ghrelin, melanocortins, and orexin as significant modulators of

alcohol seeking and consumption. The coregulation of food and alcohol intake by these signaling molecules may be based, at least in part, on the commonalities of oral intake and caloric content.

In studies aimed at determining whether hypoleptinemia contributes to the increased drug reward magnitude observed in chronically food-restricted rats, acute and chronic intracerebral infusions of exogenous leptin failed to reverse the effect of food restriction [49,50]. These experiments included direct microinjections of leptin into both the origin (midbrain ventral tegmental area) and nucleus accumbens terminus of the mesoaccumbens dopamine pathway. In fact, a regimen of continuous intraventricular leptin infusion in free-feeding rats decreased food intake and body weight and increased the reward magnitude of d-amphetamine in a manner similar to food restriction. This result not only cast further doubt on the role of hypoleptinemia but suggested that the reward-potentiating effect of food restriction is not dependent on the “stress” of food being withheld from the subject. This is an important point because stress physiology induced by food restriction is among the mechanisms hypothesized to mediate the enhancing effects on drug self-administration. A well-documented effect of food restriction is elevated circulating levels of corticosterone [51,52], although, to some extent, this reflects the metabolic role of corticosterone in releasing energy stores rather than the psychological stress of food scarcity [53–55]. Corticosterone levels in food-restricted rats have been shown to correlate with the enhanced locomotor-activating effects of cocaine and amphetamine [56–58], suppression of plasma corticosterone blocks the enhancing effect of food restriction on psychostimulant and morphine-induced hyperactivity [56], and selective ablation of the glucocorticoid receptor gene from D1 dopamine (DA) receptor-expressing neurons in mice decreases responding for cocaine [59]. Consequently, we tested stress involvement in a second way. Rats received a chronic intrac-erebroventricular infusion of a melanocortin receptor antagonist which increased food intake more than double and body weight by 30% over a two-week period. A sub-group of these subjects had their daily food allowance limited to that of untreated free-feeding rats. Consequently, they were “food-restricted”, but showed no change in the reward magnitude of d-amphetamine [50]. In a different approach to the question of endocrine regulation, behavioral testing in food restricted subjects was timed to precede or follow the single daily meal in order to compare the results obtained under 3- to 5-fold differences in circulating levels of insulin, ghrelin, and corticosterone [60]. No differences were seen in the reward magnitude of d-amphetamine or cocaine at the two time points. In a heroin self-administration protocol, Shalev and coworkers [61] demon-strated that the augmenting effect of food restriction was not affected by a CRF receptor antagonist, a glucocorticoid receptor antagonist, or adrenalectomy. Yet, these examples of negative findings with regard to the stress axis do not settle the question. Using the glucocorticoid synthesis inhibitor, ketoconazole, Carroll and coworkers [62] found that although the enhancing effect of food restriction on heroin self-administration was unaffected by the inhibitor in male rats, it was reversed by the inhibitor in females.

## 4. DOPAMINE-RELATED CHANGES UNDER BASAL CONDITIONS

While contributions of stress physiology and metabolic signaling to modulatory effects of food restriction on drug reward remain to be fully illuminated, a focus on neuroadaptations

in nucleus accumbens of food restricted subjects has yielded a set of largely coherent and functionally significant findings. The model that emerges from these studies suggests that dopamine conservation prevails under basal conditions in the food restricted subject. This is accompanied by, and perhaps responsible for, an adaptive upregulation of signaling downstream of the D1 receptor, synaptic incorporation of calcium-permeable AMPA receptors, and increased stimu-lus-induced trafficking of AMPA receptors into the nucleus accumbens postsynaptic density [63]. This set of molecular changes is hypothesized to undergird the increased incentive effects of food-related stimuli and, inadvertently, behavioral responsiveness to drugs of abuse.

To assess whether food restriction (FR) alters the excitability of mesolimbic DA cells of origin in the ventral tegmental area (VTA), voltage-clamp recordings were made in midbrain slices [64]. When DA cells were held at −70 mV, at which EPSCs are exclusively AMPAR-dependent, elicited EPSCs were lower amplitude, albeit not significantly, in VTA neurons from FR *vs*. *ad libitum* fed (AL) rats. However, when the holding potential was raised to +40 mV to reveal NMDA receptor contributions by removing the Mg2+ block of the receptor-gated channel, the EPSC amplitude was 50% lower in DA cells from FR relative to controls, confirming decreased NMDAR and/or AMPAR transmission. Next, to assess whether FR alters DA release, axonal DA release was evaluated in the intact microenvironment of the nucleus accumbens (NAc) in *ex vivo* striatal slices using fast-scan cyclic voltammetry (FCV) [65]. Evoked $[DA]_o$ in NAc shell and core was significantly lower in slices from FR subjects relative to controls. This finding agreed with the *in vivo* microdialysis results obtained by Pothos and co-workers [66,67] who found that basal levels of extracellular DA in the NAc were decreased to between 33% and 50% of the normal baseline. Together, these findings suggest that a key adaptive response to chronic FR is DA conservation. This conclusion is consistent with the fact that during food restriction and weight loss, organismic energy expenditure decreases markedly. The means of energy conservation range from reduced skeletal muscle thermogenesis to the suppression of spontaneous motor activity, which is a DA-mediated function [68].

The possibility of decreased DA utilization during FR was also investigated by taking biochemical measures [69]. Gene expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in DA bio-synthesis, was measured in VTA using both real-time RT-PCR and *in situ* hybridization. No differences were observed between diet groups. Yet, TH protein levels, determined by Western blot, were found to be elevated in NAc of FR relative to AL rats. The increase in total TH in the absence of an increase in TH synthesis is suggestive of decreased degradation and turnover. DA synthetic activity was assessed using high-performance liquid chromatography measurement of the *in vivo* tyrosine hydroxylation rate, as reflected by dihydroxyphenylalanine (DOPA) accumulation following administration of a decarboxylase inhibitor (NSD-1015). This assay revealed that DOPA accumulation in NAc was decreased by FR. While basal DA synthetic activity and utilization may be lower than control in FR subjects, the increased terminal TH protein level may represent a mechanism for priming an increase in local DA synthetic capacity without transcriptional change.

To assess the contribution of changes in the NAc DA transporter (DAT) to the net effect of FR on DA transmission, surface expression was assessed by maximal [3H] 2β-

carbomethoxy-3β-(4-fluorophenyl)-tropane binding and surface biotinylation assays [70]. No differences were seen between FR and controls. To assess whether the diet is linked to changes in DAT function, DAT kinetic parameters (Vmax and Km) were examined in NAc synaptoneuro-somes using rotating disk electrode voltammetry (RDEV), a direct measure of DA uptake in real-time. Again, no changes were seen between FR and control groups. Consequently, if the key changes in DA neurons are decreased excitability, decreased synthetic activity and decreased basal release, but with a mechanism for priming an increase in terminal synthetic capacity, this scenario may fit with the findings that acute presentation of stimuli with survival value to the FR subject, namely food (and drugs of abuse, which may be viewed as proxies for food), produce transiently higher extracellular DA concentrations in NAc of FR relative to AL rats [71–73].

Given the evidence of reduced basal DA utilization in FR subjects, downstream markers of DA receptor stimulation were measured to ascertain whether they reflected this reduction. Real-time RT-PCR was used to measure mRNA levels of neuropeptide genes in NAc [74]. Medium spiny neurons (MSNs) comprise about 95% of the NAc neuronal population, subsets of which selectively express D1, D2 or a combination of the two DA receptor types. Among the distinguishing characteristics of D1 and D2 receptor-expressing MSNs are the neuropeptides they contain. The D1R is co-expressed with dynorphin and substance P, whereas the D2R is co-expressed with enkephalin [75,76]. Consistent with the down-regulation of DA transmission, mRNA levels of preproenkephalin, preprodynorphin, and preprotachykinin were lower in FR than in control subjects, significantly so in the case of the latter two.

## 5. DOPAMINE-RELATED CHANGES UNDER STIMULATED CONDITIONS

While findings enumerated above describe aspects of the system under basal conditions, they do not explain the enhanced rewarding effects of food, its cues, and drugs of abuse in the food-restricted subject. To gain insight into this question, the system was interrogated in subjects that were challenged with acute presentation of reward stimuli including sucrose, psychostimulant drugs, and environmental cues associated with the subjective effects of drugs. An intracerebroventricular dose of d-amphetamine, shown to induce a stronger rewarding and locomotor-activating effect in FR relative to controls, was used to assess neuronal activation in NAc and other DA terminal areas using c-fos immunohisto-chemistry [77]. A greater response was observed in NAc, and several other structures, of FR relative to control subjects. In a follow-up study, this enhanced response was attributed to increased signaling downstream of the D1 receptor [78]. An intracerebroventricular dose of the D1 receptor agonist, SKF82958, shown to induce a stronger locomotor-activating effect in FR relative to controls, produced markedly greater fos-immunostaining in NAc of FR relative to controls, however, the D2 receptor agonist, quinpirole, did not.

Additional studies revealed that the full range of responses downstream of NAc D1 receptor stimulation, including intracellular signaling, neuropeptide gene expression, reward, and locomotor activation is upregulated by FR. The D1 receptor agonist, A77636, produced a greater rewarding effect in FR relative to AL fed rats, but the D2 receptor agonist, quinpirole, did not [79]. Furthermore, the D1 receptor antagonist, SCH23390, at a dose

subthreshold for affecting the rewarding and locomotor-activating effects of d-amphetamine in AL fed rats, blocked the augmenting effect of FR on both of these behavioral effects. Most tellingly, microinjection of the D1 receptor agonist, SKF82958, directly into the NAc shell produced greater rewarding and locomotor-activating effects in FR relative to AL fed rats [80]. Moreover, as would be expected based on the aforementioned finding of increased D1 receptor agonist-induced c-fos expression, intracerebroventricular administration of SKF82958 induced greater activation of extracellular signal-regulated kinase (ERK 1/2), calcium calmodulin kinase II (CaMKII), and the nuclear transcription factor, cyclic AMP response element binding protein (CREB), as determined by Western blot, in NAc of FR relative to AL fed rats [81,82]. Consistent with the increased phosphorylation of CREB, this same SKF82958 treatment was shown by real-time quantitative RT-PCR to induce markedly greater increases in levels of preprodynorphin and preprotachykinin mRNA in FR as compared to AL fed rats [74]. Interestingly, these enhanced intracellular responses to D1 receptor stimulation appear to result from recruitment of non-canonical signaling in as much as saturation binding of the D1 receptor antagonist [3H]SCH-23390 indicated no change in density or affinity of D1 binding sites [82], and stimulation of adenylyl cyclase activity by SKF82958, measured as formed cyclic AMP by radioimmunoassay, was not affected by FR [82]. On the other hand, blockade of the NMDA receptor, with MK-801, or inhibition of MEK, the enzyme upstream of ERK which is necessary for its activation, with SL-327, decreased SKF82958-induced phosphorylation of ERK and CREB, and c-fos protein expression, eliminating the difference between FR and AL fed rats [81,83]. Yet, MEK inhibition had no effect on the augmented behavioral effects of d-amphetamine or SKF82958 in FR rats [83].

The increased involvement of signaling downstream of the NMDA receptor may help explain the enhanced behavioral response of FR rats to D1 receptor stimulation. Activation of cGMP-dependent protein kinase II (cGKII) downstream of the NMDA receptor phosphorylates the AMPA receptor subunit GluA1 at Ser845, which increases GluA1 peak currents and channel open probability, and increases surface expression at extrasynaptic sites [84]. This is the penultimate step in the synaptic incorporation of AMPA receptors, which are responsible for fast excitatory synaptic transmission [85]. The possible NMDA-$Ca^{2+}$-cGKII-dependent phosphorylation of Ser845-GluA1 would be convergent with the expected and separate PKA-dependent phosphorylation that occurs downstream of D1 receptor-dependent adenylyl cyclase activation [86,87].

## 6. AMPA RECEPTOR TRAFFICKING UNDER BASAL AND STIMULATED CONDITIONS

To test the prediction that reward stimuli induce greater Ser845-GluA1 phosphorylation in NAc of FR relative to AL fed rats, subjects were challenged with the D1 receptor agonist, SKF82958, or d-amphetamine, or consumed ~12 ml of 10% sucrose. Twenty minutes later, levels of pSer845-GluA1, as determined by Western blot, were shown to be increased by these stimuli with a markedly greater effect in FR rats [88–90]. Using a subcellular fractionation method, it was also shown that these reward stimuli rapidly increased the abundance of GluA1 and GluA2 in the NAc postsynaptic density (PSD), suggesting synaptic

strengthening, again with a greater effect in FR rats [88,90]. No changes were seen in the abundance of the GluA3 subunit or the control synaptic protein, PSD95. Given that the majority of AMPA receptors in NAc are either GluA1/GluA2 or GluA2/GluA3 heteromers [91], it seems likely that reward stimuli induce synaptic incorporation of GluA1/GluA2 downstream of pSer845-GluA1, and that this form of synaptic plasticity is upregulated by FR.

In the course of investigating the effects of reward stimuli on AMPAR trafficking, it was discovered that FR, alone, increases NAc synaptic abundance of GluA1. Using a $BS^3$ cross-linking method, in which surface receptors are covalently cross-linked to nearby proteins using the membrane-impermeable $BS^3$ [92], thereby increasing their molecular weight relative to intracellular receptors, it was shown that FR increases surface expression of GluA1, but not GluA2 [93]. Subcellular fractionation localized the increased GluA1 abundance to the PSD. These findings suggested that FR increases the synaptic insertion of GluA2-lacking, calcium-permeable AMPA receptors (CP-AMPARs), which are relatively rare. This conclusion was substantiated by electrophysiological findings in striatal slices in which Naspm, a selective antagonist of CP-AMPARs, decreased the amplitude of evoked EPSCs in NAc MSNs of FR, but not AL, rats. CP-AMPARs have a number of distinct properties relative to other AMPAR types, including larger single-channel conductance, faster kinetics, and triggering of post-synaptic signaling cascades that depend on $Ca^{2+}$ [94]. A context in which synaptic incorporation of CP-AMPARs has been well studied is homeostatic synaptic scaling, occurring in response to a sustained deprivation of excitatory input [95,96]. Particularly germane to the molecular events described in NAc of FR rats are findings that in cultured striatal MSNs, a cooperative relationship exists between CP-AMPARs and D1Rs in regulating phosphorylation and trafficking of AMPARs. Briefly, D1R stimulation increases phosphorylation of GluA1 at Ser845, *via* protein kinase A (PKA), thereby increasing extrasynaptic accumulation of GluA1-containing AMPARs [97]. Concurrent stimulation of CP-AMPARs triggers intracellular $Ca^{2+}$ signaling, activating cyclic GMP and cyclic GMP-dependent protein kinase II, which augment the phosphorylation of GluA1 at Ser845, and is followed by protein kinase C-mediated synaptic insertion of GluA1 and GluA2. Thus, both the increased signaling downstream of NMDA receptors and a cooperative relationship between D1 and CP-AMPARs in NAc of FR rats may play a role in the increased reward stimulus-induced phos-phorylation at Ser845-GluA1 and subsequent trafficking of AM-PARs into the postsynapse. In fact, it may be the presence of CP-AMPARs and their voltage-independent conductance that facilitates a depolarization of MSNs sufficient to relieve the magnesium block of NMDA receptors and thereby enable voltage-dependent conductance in the NAc of FR subjects more so than in AL subjects [98].

*In vivo*, NAc synaptic insertion of CP-AMPARs occurs during long term withdrawal from cocaine and mediates the incubation of craving, thereby contributing to relapse risk [99]. In order to evaluate the contribution of CP-AMPARs to the behavioral effects of FR, Naspm was microinjected into NAc as was done in the studies of co-caine craving. These experiments supported the role of CP-AMPARs in the enhanced responses of FR subjects to drug administration [88,93]. Microinjection of Naspm into NAc shell reversed the enhanced rewarding effects of SKF82958 and d-amphetamine, and reversed the enhanced locomotor-activating effect of SKF82958 in FR subjects, having no effects in AL fed subjects. Naspm

also had no effect on the rewarding or locomotor-activating effects of the D2 receptor agonist, quinpirole, regardless of diet.

## 7. ON THE ROLE OF REWARD DEFICIT AND MEDIUM SPINY NEURON SUBTYPES

To summarize the findings outlined above, studies of the mesolimbic pathway in FR rats have produced evidence of decreased basal DA utilization, and increased intracellular signaling, gene expression and behavior downstream of D1 receptor stimulation. These upregulated responses involve CP-AMPARs and NMDA receptors, and enable increased reward stimulus-induced synaptic incorporation of AMPARs paralleling augmented behavioral responses. However, many important questions remain to be addressed. For example, it is not known what role sustained reward deficit, as opposed to an energy deficit, may play in the molecular adaptations to FR. There are several other conditions that may be described as “sustained loss of reward” and are associated with synaptic incorporation of CP-AMPARs in NAc. These include several weeks’ withdrawal from chronic cocaine [99], amphetamine [100], and ‘junk food’ [101]. Thus, synaptic incorporation of CP-AMPARs in NAc may be a homeostatic response to severe and sustained reward loss. This hypothesis implies that the neurochemical concomitant of reward loss in FR rats, namely decreased DA transmission, is the stimulus for CP-AMPAR insertion; though, as suggested above, decreased DA transmission is also an underpinning of homeostatic energy conservation. Whether a decrease in DA transmission is sufficient to induce synaptic incorporation of CP-AMPARs is not known. It has, however, been reported that progressive and chronic DA depletion in a genetic mouse model of Parkinson’s Disease produces increased dorsal striatal levels of GluA1 and pSer845-GluA1 [102], and DA depletion induced by 6-OHDA treatment increases synaptic incorporation of CP-AMPARs [103], though it must be borne in mind that the DA deficiency in those models is more severe than any adaptive downregulation that may occur in the FR subject.

In addition to depressed DA transmission as a possible triggering condition for the AMPAR trafficking effects of FR, it is possible that elevated corticosterone, ghrelin, and/or hypoleptinemia have a role as well. The supporting evidence for each comes primarily from work on brain regions other than NAc. For example, in hippocampal cultures and slices, corticosterone produces a glucocorticoid receptor-mediated increase in synaptic GluA1 and GluA2 [104,105], and in cultured rat prefrontal cortex neurons, corticosterone increases dendritic GluA1 surface expression and synaptic clustering [106]. Moreover, in the hippocampus, ghrelin has been shown to increase synaptic incorporation of GluA1 and synaptic strengthening [107]. However, unlike the hippocampus, NAc may be devoid of ghrelin receptor mRNA [108]. While increased leptin exposure rather than hypoleptinemia is the condition that increases the synaptic density of GluA1 in hippocampal slices [109], leptin microinjection in NAc blocked cocaine-induced phosphorylation of GluA1 at Ser845 [110]. This finding raises the possibility that hypoleptinemia contributes to the enhancement of basal and stimulated phosphorylation at Ser845, which is a precondition for synaptic insertion of CP-AMPARs as well as stimulus-induced synaptic insertion of GluA1-containing heteromers [86, 94, 96].

Another important outstanding question concerns the phenotype of MSNS that are subject to FR-induced synaptic incorporation of CP-AMPARs. Pharmacological findings suggest that the AMPAR mechanisms involved in increased reward magnitude operate preferentially or exclusively in D1 receptor-expressing MSNs. How-ever, this question has not been addressed directly in any experiment. Should this prove to be the case, it would be consistent with the literature, based in large part on use of optogenetic methods, which attribute incentive motivation and reward enhancing effects to excitation of D1 receptor-expressing MSNs, while opposite effects have been attributed to excitation of D2 receptor expressing MSNs [111–113, 114].

## 8. GLUTAMATERGIC INPUTS TO NUCLEUS ACCUM-BENS

If AMPA receptor signaling is essential for the enhanced rewarding effects of dopamine-releasing stimuli, the source and circumstance of glutamate release must be identified as well. Reward learning, goal-directed behavior, and addiction are all undergirded by the convergence of glutamatergic and dopaminergic inputs to NAc [115–117], with three major sources of glutamatergic input; namely prefrontal cortex, basolateral amygdala, and ventral hippo-campus [118–121]. Additional glutamatergic input, though some-what less well studied, arises from paraventricular thalamus [121–123]. It is not known whether one, a subset, or all of these inputs interact with CP-AMPARs in NAc of FR rats to generate increased drug reward magnitude. However, it is of interest to note that 95% of all NAc MSNs are excited by input from each of these afferent pathways [124], and optogenetic stimulation of terminals from each within NAc is rewarding [124–126]. Consequently, it may be the case that all glutamatergic inputs to NAc have the potential to interact with a behaviorally significant population of CP-AMPARs, with the driving input at any given time varying according to context and the specific behavior being expressed.

Also to be considered is a simpler scenario in which upregulated NAc reward signaling can be achieved in response to input from the VTA DA cell group alone. It has recently been established that a subset of VTA neurons co-release dopamine and glutamate, causing synchronous activation of postsynaptic DA and glutamate receptors, and excitatory responses in MSNs [127–130]. Thus, concurrent activation of D1 and CP-AMPARs may not require input to NAc from a forebrain source.

## 9. POSSIBLE IMPLICATIONS FOR NEUROPLASTICITY AND MALADAPTIVE BEHAVIOR

Finally, stimulus-induced synaptic insertion of AMPARs is not only a mechanism for dynamic tuning of synaptic transmission [131] but also an established underpinning of synaptic plasticity that leads to long term changes in neurocircuit function and behavior, including addiction [132,133]. This raises the question of whether reward learning that takes place during FR is more likely to become established or is more strongly established than when it occurs under the condition of AL feeding. This question has yet to be investigated but may lead to the improved mechanistic under-standing of how breakthrough gorging during periods of severe dieting increases the risk for future binge pathology

[134,135], and the high addictive potential of anorexigenic stimulants, such as nicotine and methamphetamine, which invariably leads to bodyweight loss.

## 10. RESEARCH WITH LABORATORY ANIMALS

All research from the author's laboratory, summarized here, was approved by the New York University School of Medicine Institutional Animal Care and Use Committee and performed in accordance with the "Principles of Laboratory Animal Care" (NIH publication number 85–23).

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