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Chronic food restriction: Enhancing effects on drug reward and striatal cell signaling

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Abstract

Chronic food restriction (FR) increases behavioral sensitivity to drugs of abuse in animal models and is associated with binge eating, which shares comorbidity with drug abuse, in clinical populations. Behavioral, biochemical and molecular studies conducted in this laboratory to elucidate the functional and mechanistic bases of these phenomena are briefly reviewed. Results obtained to date indicate that FR increases the reward magnitude and locomotor-activating effects of abused drugs, and direct dopamine (DA) receptor agonists, as a result of neuroadaptations rather than changes in drug disposition. Changes in striatal DA dynamics, and postsynaptic cell signaling and gene expression in response to D-1 DA receptor stimulation have been observed. Of particular interest is an upregulation of NMDA receptor-dependent MAP kinase and CaM Kinase II signaling, CREB phosphorylation, and immediate-early and neuropeptide gene expression in nucleus accumbens (NAc) which may facilitate reward-related learning, but also play a role in the genesis of maladaptive goal-directed behaviors. Covariation of altered drug reward sensitivity with body weight loss and recovery suggests a triggering role for one of the endocrine adiposity hormones. However, neither acute nor chronic central infusions of leptin or the melanocortin 3/4 receptor agonist, MTII, have attenuated *d*-amphetamine reward or locomotor activation in FR rats. Interestingly, chronic intracerebroventricular leptin infusion in ad libitum fed (AL) rats produced a sustained decrease in food intake and body weight that was accompanied by a reversible potentiation of rewarding and locomotor-activating effects of *d*-amphetamine. This raises the interesting possibility that rapid progressive weight loss is sufficient to increase behavioral sensitivity to drugs of abuse. Whether weight loss produced by leptin infusion produces the same neuroadaptations as experimenter-imposed FR, and whether any of the observed neuroadaptations are necessary for expression of increased behavioral responsiveness to acute drug challenge remain to be investigated.

Keywords: Food restriction; Reward; Addiction; Binge eating; Nucleus accumbens; Dopamine; MAP kinase

A long-standing and widely held hypothesis contends that drugs of abuse exert their reinforcing effects by activating neuronal circuits that normally reinforce survival behaviors of the organism. Some of the earliest findings lending support to this hypothesis followed the discovery of intracranial electrical self-stimulation and the brain reward system [1]. In key studies, the threshold intensity or frequency of electrical stimulation required to reinforce the self-stimulation response was decreased either by providing concurrent orosensory stimulation with sucrose [2,3] or administering a drug of abuse [4,5]. These findings suggested that medial forebrain bundle electrodes tap into a unitary reward system that is responsive to natural incentive stimuli but also serves as the target tissue for drugs with abuse liability. In recent years, abundant behavioral and neurobiological evidence of a close association between food and drug intake has been obtained. In several studies, animals' avidity for sweet solution has predicted behavioral responsiveness to drugs of abuse [6–10], and rats selectively bred for high saccharin intake have displayed enhanced drug self-administration and relapse to drug-seeking following extinction [11]. Availability of saccharin solution, as an alternative reinforcer, decreases self-administration of abused drugs [e.g., 12], and brief pre-exposure to sweet solution decreases cocaine self-administration and its reinstatement [13]. On the other hand, chronic intermittent exposure to sucrose sensitizes rats to the locomotor-activating effect of a future psychostimulant drug challenge [14,15].

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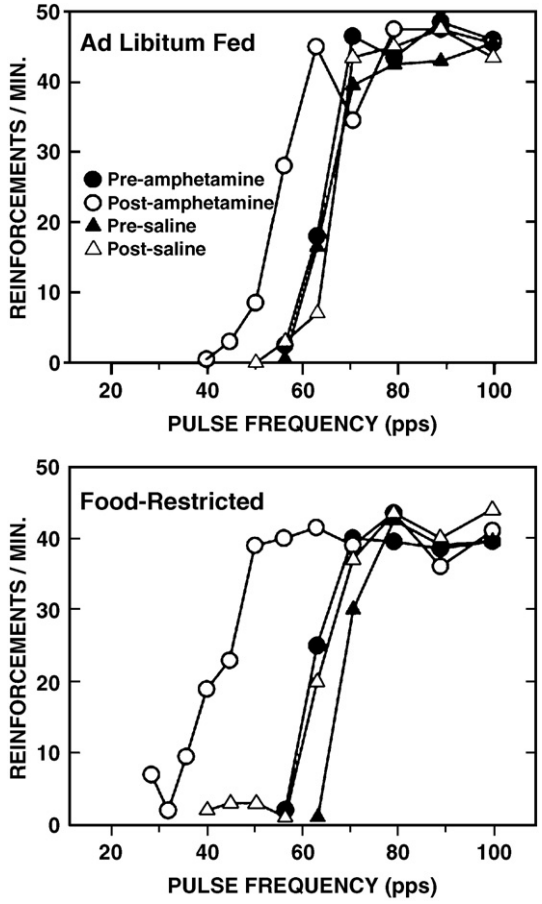

Fig. 1. Lateral hypothalamic self-stimulation rate–frequency curves were generated by allowing subjects to lever press for 1-sec trains of brain stimulation with stimulation frequency decreasing systematically over a series of 1-min trials. This figure displays a set of representative rate–frequency curves for an ad libitum fed (AL; top) and a food-restricted (FR; bottom) rat immediately prior to and 10 min following injection of *d*-amphetamine (0.5 mg/kg, i.p.) or saline vehicle. The standard food restriction regimen of this laboratory is one in which daily food intake is limited to 10 g of chow until body weight decreases by 20–25% (2–3 weeks). Body weight is then maintained at this level throughout the period of behavioral testing by titrating daily food allotment. In both rats, *d*-amphetamine shifted the curves to the left, lowering the reward threshold (i.e. stimulation frequency supporting 50% of the maximal reinforcement rate). The FR rat displayed the characteristic enhancement of *d*-amphetamine's threshold-lowering (i.e. rewarding) effect. Similar results were obtained when *d*-amphetamine or other drugs, including cocaine and d-pen-d-pen-enkephalin, were injected into the brain ventricular system (see text). This figure is adapted from one previously published [40] with the kind permission of the Society for Neuroscience (Copyright 1998).

Separate neurons, that are evenly distributed throughout the nucleus accumbens (NAc), fire in association with instrumental responding for food/water versus cocaine [16], and the neuronal activity that correlates with reward-seeking is dependent upon dopamine (DA) input from the ventral tegmental area [17]. It is therefore of interest that extracellular DA concentrations in NAc are increased in a concentration/dose-related manner by sucrose licking [18] and passively administered drugs of abuse [19]. Further, subsecond measurements of DA release in NAc indicate that peak DA signals coincide with initiation of lever pressing for both cocaine and sucrose reward [20,21]. It has been hypothesized that drug addiction involves plastic changes in NAc neuronal excitability such that food- and other natural goal-responsive cells become inhibited while drug task-responsive cells retain excitability [22].

One of the most thoroughly investigated behavioral phenomena indicative of an association between mechanisms regulating

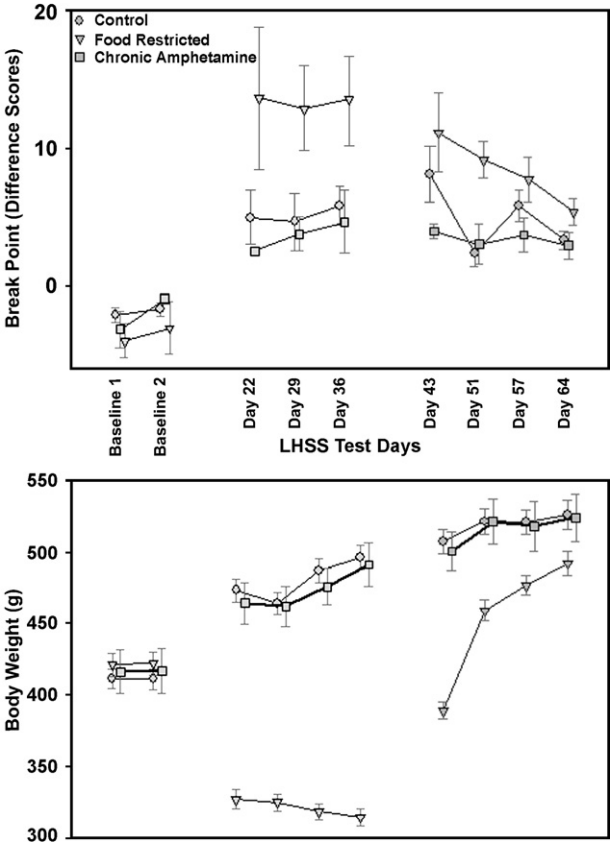

Fig. 2. A progressive ratio protocol was used to measure the break point-increasing effect of *d*-amphetamine (0.25 mg/kg, i.p.) on responding for lateral hypothalamic electrical stimulation. Results are expressed (top) as difference scores (i.e., break point on the test immediately following *d*-amphetamine injection minus break point on an identical test immediately preceding *d*-amphetamine injection) for three groups of subjects. AL control subjects (filled circles) always had free access to food and their only exposure to *d*-amphetamine was on the test days indicated (i.e., days 22, 29, 36, 43, 51, 57, 64 of the experiment). FR subjects (filled triangles) were maintained on the laboratory's standard food restriction regimen (see Fig. 1 legend) for 21 days prior to initiation of *d*-amphetamine testing, and continued on that regimen through day 40, after which AL access to food was reinstated. Chronic *d*-amphetamine-treated subjects (filled squares) always had free access to food but on days 14–18 received a regimen of *d*-amphetamine treatment (5 mg/kg/day × 5 days) that was verified to produce persistent, escalating locomotor sensitization in a separate group of subjects. Mean (±s.e.m.) body weights of all three groups are displayed (bottom). "Baseline" in the top graph relates to the effects of saline vehicle injection on days 19 and 21; in the bottom graph it relates to body weights of the three groups three days and one day prior to implementation of the FR regimen and 23/25 days prior to initiation of *d*-amphetamine testing. FR enhanced the break point-increasing effect of *d*-amphetamine, and the effect was reversible in tandem with body weight recovery when AL access to food was reinstated. A "sensitizing" regimen of *d*-amphetamine pretreatment had no effect. This figure is adapted from one previously published [47] with the kind permission of the Springer Verlag (Copyright 2004).

food and drug intake is the enhancement of drug self-administration by chronic food restriction (FR). Carroll and colleagues have demonstrated that FR enhances acquisition of drug self-administration behavior, lowers the threshold reinforcing dose, increases the amount of behavioral effort subjects are willing to expend, and increases the amount of drug consumed [e.g., 23–25]. The robustness of this effect is illustrated by the finding that genetic strain differences in sensitivity to locomotor and reinforcing effects of amphetamine in mice can be abolished by imposing FR upon the less sensitive strain [26]. While these effects of FR are likely to reflect adaptations that otherwise promote food seeking, acquisition and ingestion, increased responsiveness to drugs of abuse is not the only maladaptation that may result from FR. In clinical populations, food restriction is associated with the development and persistence of binge eating disorder [27,28], and there is a well-documented high comorbidity of binge eating and drug abuse [29–32]. Moreover, the relationship between eating behavior and drug abuse is not limited to clinical populations. In a large sample of incoming female college students, a positive and continuous relationship was observed between dieting severity and prevalence of drug and alcohol use [33]. In a recent animal model, multiple brief episodes of FR have been shown to increase vulnerability to stress-induced binge eating of palatable foods [34].

1. Effects of chronic FR on measures of drug reward and reward seeking

Early results of this laboratory indicated that chronic FR lowers the electrical brain stimulation reward threshold, in perifornical hypothalamic sites, in a manner that covaries with body weight, suggesting that negative energy balance, and perhaps adipose depletion in particular, triggers neuroadaptations in brain reward circuitry [35]. Subsequent studies implicated endogenous opioid mechanisms [36] and the endocrine adiposity hormones, leptin [37] and insulin [38] in this effect. To specifically investigate the interaction between FR and drugs of abuse, a psychophysical curve-shift method was used to measure sensitivity of brain reward circuitry to direct electrical stimulation immediately prior to and following administration of a variety of abused drugs. Drugs with abuse liability, and documented reinforcing effects in self-administration and place preference assays, produce dose-related leftward shifts in the curve that relates rate of reinforcement to the brain stimulation frequency for which the animal is responding [39]. The extent of leftward shift is a reliable and sensitive measure of drug reward magnitude, while changes in asymptote or slope of the rate–frequency curve are indicative of changes in performance factors. The ability of this method to distinguish between treatment effects on reward and performance allowed the conclusion that FR specifically increases drug reward magnitude (Fig. 1) [40]. Furthermore, the finding that drugs administered via the intracerebroventricular (i.c.v.) route were as fully subject to the enhancing effect as systemically administered drugs strongly suggested that FR increases central sensitivity rather than altering drug disposition [40–42]. This point is important, considering that all prior studies of drug self-administration in FR subjects had involved systemic routes of administration, and there are numerous physiological concomitants of FR that may alter the bioavailability and pharmacokinetics of systemically administered drugs [43–46]. The enhancing effect of FR was also demonstrated in a progressive ratio protocol of self-stimulation testing in which *d*-amphetamine produced a markedly greater increase in break point in FR relative to AL rats [47]. Of further interest was the finding that a "sensitizing" regimen of *d*-amphetamine treatment, verified to produce locomotor sensitization in AL rats, did not alter the break point-increasing effect of *d*-amphetamine in this protocol (Fig. 2). This latter result represents one of the several findings pointing to a functional and mechanistic difference

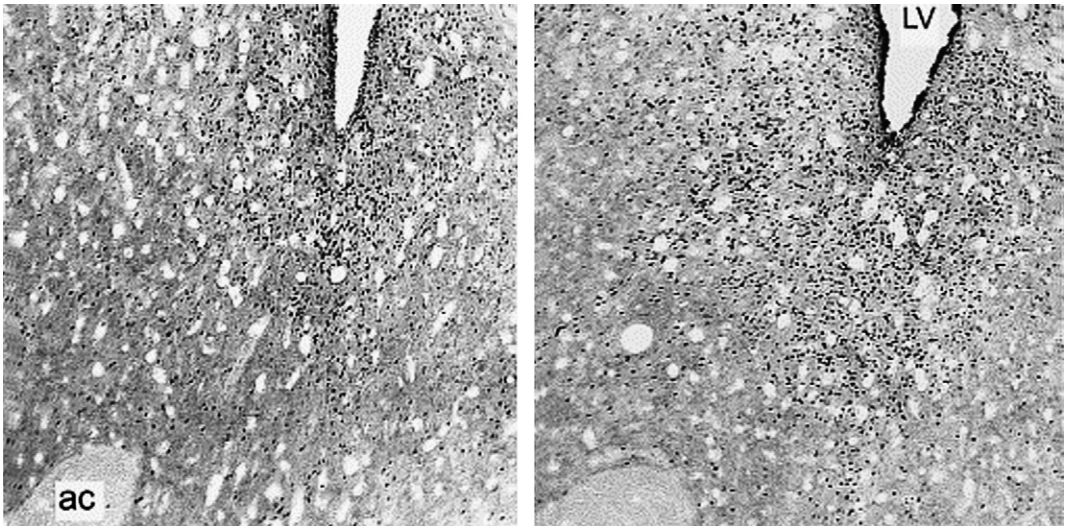

Fig. 3. Fos-like immunoreactivity (FLI) in the nucleus accumbens of a representative AL subject (left) and FR subject (right) injected i.c.v. with a dose of *d*-amphetamine (50 μg) that had produced greater rewarding and locomotor-activating effects in FR relative to AL rats in a previous study (see text). Significantly greater FLI was observed in FR subjects. ac = anterior commissure, LV = lateral ventricle. This figure is adapted from one previously published [55] with the kind permission of Elsevier Science Ltd. (Copyright 2000).

between psychostimulant-induced sensitization and the enhancing effect of FR. Another distinguishing characteristic is the reversibility of the latter, with body weight recovery [42,47], versus the indefinite persistence of the former [48–51].

The diversity of drugs affected by FR, including psychostimulants, opioids, and dissociative anesthetics, suggested that the underlying neuroadaptations are likely to exist within a "final common pathway" for drug reward — a role commonly ascribed to mesoaccumbens DA neurons and NAc microcircuitry [e.g., 52–54]. We therefore examined the neuroanatomical pattern and density of Fos-immunostaining produced by an i.c.v. dose of *d*-amphetamine that had behaviorally differentiated FR and AL rats in the brain reward and locomotor activity tests. While basal Fos-immunostaining did not differ between feeding groups in most brain regions examined, *d*-amphetamine produced greater Fos-immunostaining in a variety of subcortical DA terminal areas – including NAc, caudate–putamen (CPu), central amygdala, bed nucleus of the stria terminalis, and ventral pallidum – of FR relative to AL rats (Fig. 3) [55]. These results not only provided cellular correlates of the increased behavioral responsiveness to *d*-amphetamine in FR subjects but were suggestive of a global change in the brain DA system. Evidence of altered DA dynamics in striatal regions of FR subjects had previously been reported. For example, in microdialysis studies, basal extracellular DA concentrations in NAc were decreased [56], but salient stimuli, such as food and drugs of abuse, produced higher extracellular DA concentrations in NAc of FR relative to AL rats [57–59]. More recently, the higher extracellular DA concentration produced by psychostimulants in FR rats was localized to NAc core [60]. In addition, 36 h of total food deprivation was shown to decrease V_{max} of the DA transporter in CPu, though not in NAc [61], and, more recently, the chronic FR regimen used in this laboratory was verified to decrease V_{max} of the striatal DA transporter [62].

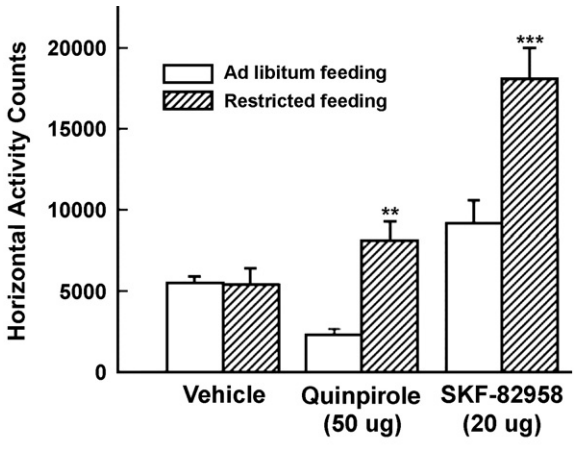

Fig. 4. Locomotor activation measured as mean (±s.e.m.) number of horizontal activity counts (photobeam interruptions) during a 30-min period, 5 min following i.c.v. injection of the D-2 DA agonist, quinpirole (50 μg), the D-1 DA agonist, SKF-82958 (20 μg) or saline vehicle. Repeated measurements were taken on AL (open bars) and FR (filled bars) rats. FR markedly increased the locomotor response to both agonists (see text). This figure is reproduced from a previous publication [64] with the kind permission of Elsevier Science Ltd. (Copyright 2003).

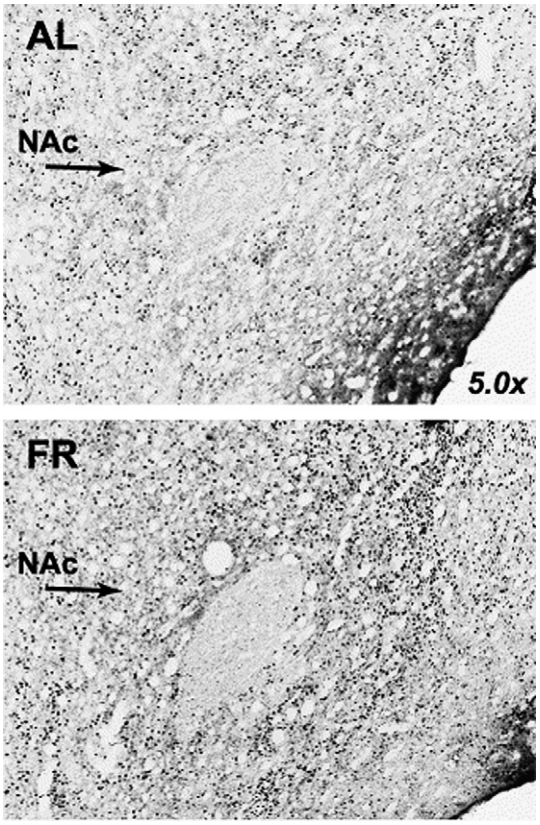

Fig. 5. Fos-like immunoreactivity (FLI) in the nucleus accumbens of a representative AL (top) and FR subject (bottom) injected i.c.v. with the same dose of the D-1 DA agonist, SKF-82958 (20 μg), that had produced a greater locomotor-activating effect in FR relative to AL rats (see Fig. 4 and text). Significantly greater FLI was observed in FR subjects. This figure is adapted from one previously published [64] with the kind permission of Elsevier Science Ltd. (Copyright 2003).

It was reasoned that if the critical neuroadaptations produced by FR in the brain DA system are primarily presynaptic, repetition of this laboratory's behavioral and immunohistochemical experiments, using direct D-1 and D-2 DA receptor agonists, should yield little or no difference between feeding groups. Contrary to this prediction, the selective D-1 DA receptor agonists A-77636 and SKF-82958, and the D-2 DA receptor agonist, quinpirole, produced greater rewarding and locomotor-activating effects in FR than AL rats (Fig. 4) [63,64]. In addition, i.c.v. doses of SKF-82958 and quinpirole that differentiated the feeding groups behaviorally, produced greater Fos-immunostaining in a number of subcortical DA terminal areas of FR rats, with the D-1 agonist producing prominent differences between groups in NAc and CPu (Fig. 5) [64]. These findings suggested that behaviorally important neuroadaptations exist postsynaptically in DA terminal areas and prompted a closer examination of D-1 DA receptor binding and signal transduction.

2. D-1 DA receptor binding, signal transduction, and neuropeptide gene expression

In agreement with the results of a previous autoradiographic study [56], radiologand binding assays, using the D-1 DA

receptor antagonist [^{3}H]SCH-23390, indicated no difference between FR and AL subjects with regard to the density or ligand affinity of binding sites in CPu or NAc [65]. Further, unlike behavioral sensitization induced by chronic psychostimulant treatment and stress [e.g., 66,67], stimulation of adenylyl cyclase activity by SKF-82958 in CPu and NAc was not increased by FR [64]. However, forskolin-stimulated adenylyl cyclase activity was lower in both brain regions of FR relative to AL rats, with no difference in stimulation by $MnCl_2$. Because stimulation by $MnCl_2$ does not require association of adenylyl cyclase with G_s-protein, while stimulation by forskolin does [68,69], this finding may indicate that FR changes the balance of expression among adenylyl cyclase isoforms, which are known to differ in sensitivity to forskolin stimulation and may affect the degree of interaction between signal transduction pathways [70].

In light of the reports that behavioral and cellular supersensitivity to direct DA receptor agonists can be mediated by an upregulation or switch to MAP kinase signaling [71,72], a series of experiments was conducted to evaluate D-1 DA receptor agonist-induced MAP kinase activation in FR subjects. Using the same dose and i.c.v. route of administration as in the preceding behavioral and Fos-immunohistochemical experiments, SKF-82958 produced a markedly greater phosphorylation of ERK-1 and ERK-2 in both the CPu and NAc of FR relative to AL rats (Figs. 6 and 7) [65]. Interestingly, i.c.v. injection of saline vehicle also produced a greater activation of ERK 1/2 in the NAc of FR than AL rats, albeit significantly less than produced by SKF-82958. The activation by vehicle injection does not represent the basal state of FR rats because ERK 1/2 phosphorylation did not differ between feeding groups when animals were undisturbed prior to sacrifice. It is possible that the MAP kinase pathway in NAc of FR rats is also hyperresponsive to the stressful aspect of the i.c.v. microinjection procedure, although the mediating receptor type(s) is not known. No differences were observed between groups in protein levels of the major phosphatases, MKP-2 or PP1, although the catalytic activity of these enzymes was not evaluated. Among potential downstream targets of the upregulated MAP kinase signaling, increased activation of the nuclear transcription factor, CREB (Fig. 8) [65], and increased preprodynorphin and preprotachykinin gene expression were observed in response to D-1 DA receptor agonist administration in FR rats (Fig. 9) [73].

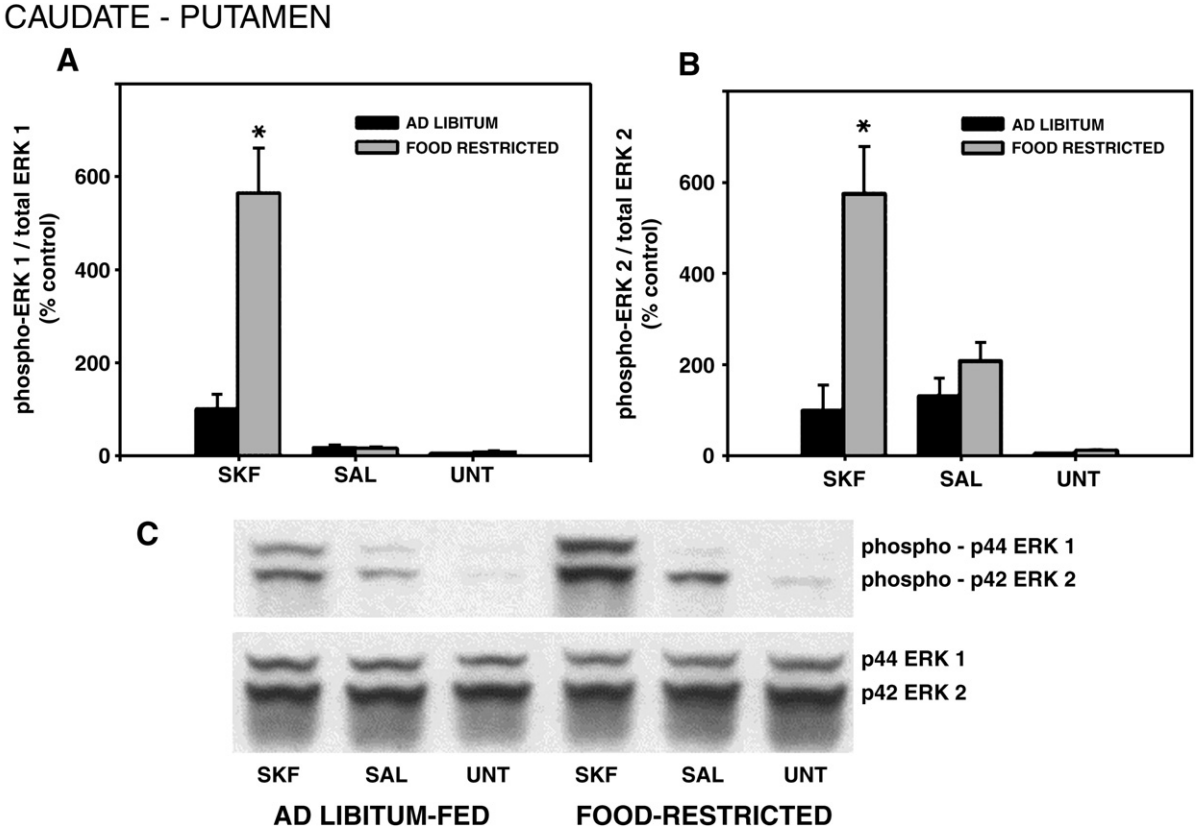

Fig. 6. Effects of FR on ERK 1/2 MAPK phosphorylation in caudate–putamen. Subjects were injected i.c.v. with the same dose of the D-1 DA agonist, SKF-82958 (20 μg), that had produced a greater locomotor-activating effect and striatal Fos-like immunostaining in previous experiments (see Figs. 4, 5 and text), saline vehicle, or were untreated (UNT) prior to sacrifice. Lysates were immunoblotted with anti-phospho p44/42 MAPK or anti-p44/42 MAPK antibodies. Following densitometry, intensities of bands corresponding to phospho-ERK 1 and 2 for each subject were divided by the intensities of the corresponding total ERK bands to correct for small differences in protein loading. Results (mean±s.e.m.) are expressed in comparison to the normalized control, which was defined as the AL group injected with SKF-82958. Results are displayed for pERK1 (A) and pERK2 (B) with representative immunoblots (C). FR markedly increased activation of ERK 1/2 in response to SKF-82958 but did not alter total ERK 1/2 (lower set of bands). This figure is reproduced from a previous publication [65] with the kind permission of Elsevier Science Ltd. (Copyright 2004).

3. NMDA receptor involvement in signaling responses to D-1 DA receptor stimulation and relation to mechanisms involved in synaptic plasticity

In striatal medium spiny neurons, the D-1 DA and NMDA glutamate receptors are coexpressed [74,75] and are functionally associated in controlling excitatory synaptic currents [76,77], signal transduction [78], gene expression [79], and instrumental [80] and Pavlovian [81] learning. Most importantly, NMDA receptor stimulation activates the ERK cascade [for review, see Ref. [82]], and stimulation of the D-1 DA receptor leads to phosphorylation of the NMDA receptor NR1 subunit [83], thereby increasing Ca^{2+} flux through the cation channel and recruiting NMDA receptor-linked signal transduction pathways [78]. Consequently, in the next set of experiments we focused on the possible involvement of the NMDA receptor in D-1 DA agonist-induced cell signaling. It was found that i.c.v. injection of SKF-82958 produced greater phosphorylation of the NMDA NR1 subunit in NAc of FR relative to AL rats, as well as greater activation of CaMK II (Fig. 10) [84]. Further, pretreatment of subjects with a systemic injection of the NMDA antagonist, MK-801, decreased SKF-82958-induced activation of CaMK II, ERK 1/2, and CREB, and abolished the enhancing effect of FR on activation of all three proteins (Fig. 11). Finally, SL-327, an inhibitor of MEK — the kinase upstream of ERK 1/2, suppressed SKF-82958-induced activation of ERK 1/2 and reversed the enhancing effect of FR on CREB activation. These results suggest specific neuroadaptations in the NAc of FR rats whereby D-1 DA receptor stimulation leads to increased NMDA receptor function and consequent increases in NMDA receptor-dependent CaMK II and ERK 1/2 signaling, and downstream activation of the nuclear transcription factor, CREB. The increased *c-fos*, preprodynorphin and preprotachykinin gene expression that have been observed are likely to be among the downstream functional consequences.

The potential involvement of increased MAP kinase signaling in the enhanced behavioral and *c-fos* responses to psychostimulant and D-1 DA agonist challenge in FR rats is supported by a number of recent studies. A wide range of abused drugs activate ERK throughout the striatum [85], the ERK cascade activates transcription factors (CREB, Elk-1) that bind to the promoter region of the *c-fos* gene [86], and MEK inhibitors decrease the conditioned place preference otherwise reinforced by cocaine,

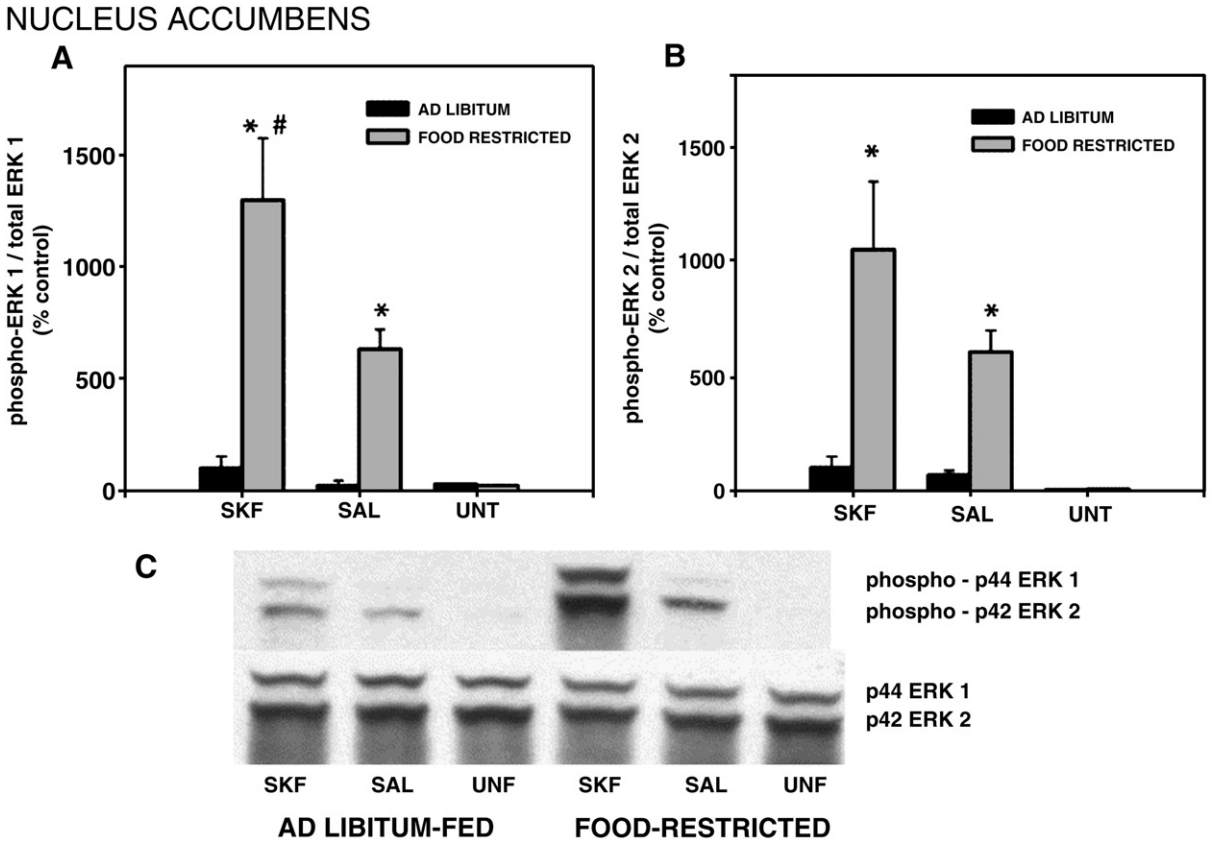

Fig. 7. Effects of FR on ERK 1/2 MAPK phosphorylation in nucleus accumbens. Subjects were injected i.c.v. with the same dose of the D-1 DA agonist, SKF-82958 (20 μg), that had produced a greater locomotor-activating effect and striatal Fos-like immunostaining in previous experiments (see Figs. 4, 5 and text), saline vehicle, or were untreated (UNT) prior to sacrifice. Lysates were immunoblotted with anti-phospho p44/42 MAPK or anti-p44/42 MAPK antibodies. Following densitometry, intensities of bands corresponding to phospho-ERK 1 and 2 for each subject were divided by the intensities of the corresponding total ERK bands to correct for small differences in protein loading. Results (mean ± s.e.m.) are expressed in comparison to the normalized control, which was defined as the AL group injected with SKF-82958. Results are displayed for pERK1 (A) and pERK2 (B) with representative immunoblots (C). FR markedly increased activation of ERK 1/2 in response to SKF-82958 but did not alter total ERK 1/2 (lower set of bands). FR also increased activation in response to saline vehicle, though the response was significantly weaker than the response to SKF-82958 (see text). This figure is reproduced from a previous publication [65] with the kind permission of Elsevier Science Ltd. (Copyright 2004).

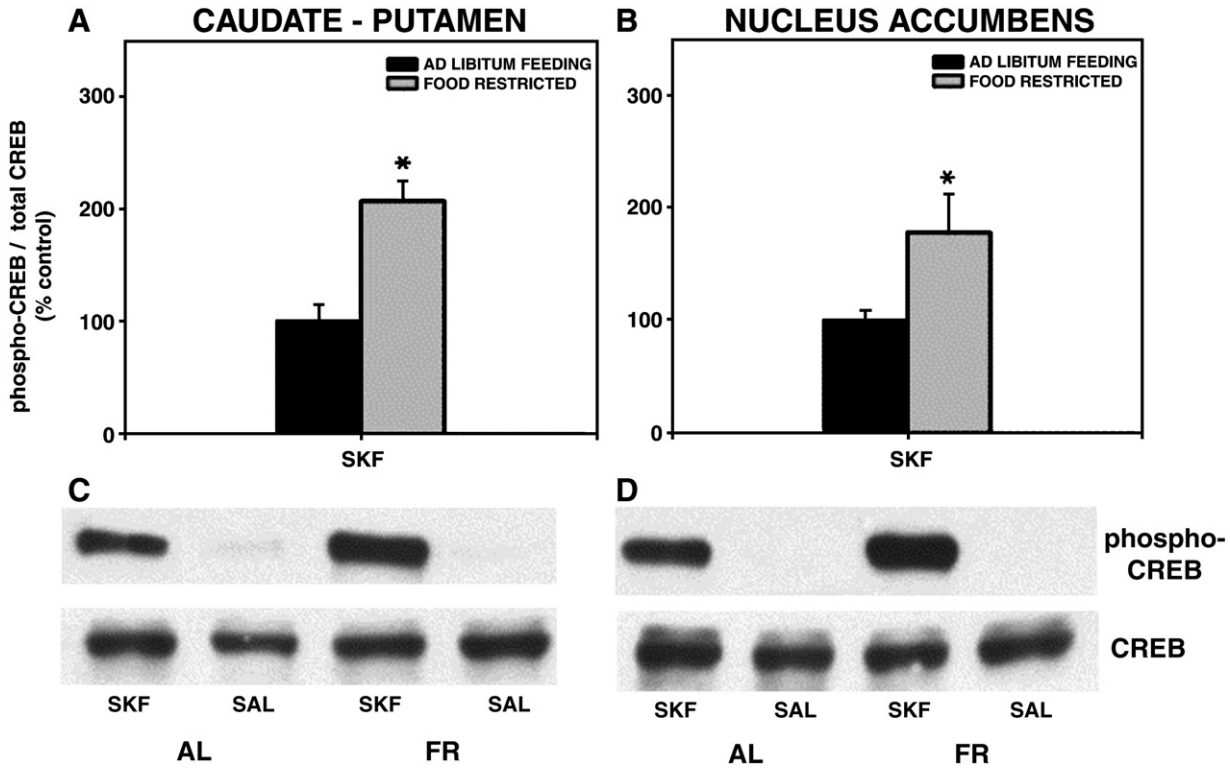

Fig. 8. Effects of FR on CREB phosphorylation in CPu and NAc. Lysates were immunoblotted with anti-phospho CREB or anti-CREB antibodies. The mean (±s.e.m.) ratios of pCREB/total CREB, as determined by densitometric scanning, are expressed in comparison to the normalized control and displayed for CPu (A and C) and NAc (B and D). FR increased the activation of CREB in response to SKF-82958 but did not alter total CREB (lower set of bands). At exposure times necessary to obtain strong pCREB bands in SKF-82958-treated subjects, pCREB bands were not detectable in subjects of either feeding group injected with saline vehicle. This figure is reproduced from a previous publication [65] with the kind permission of Elsevier Science Ltd. (Copyright 2004).

amphetamine, THC and MDMA [87–90]. It is also important to note that the NMDA–ERK–CaMK II pathway, which appears to be upregulated in the NAc of FR subjects, has been implicated in learning, memory and neuroplasticity. In the hippocampal model, long term potentiation (LTP) is mediated by increased Ca^{2+} conductance through the NMDA cation channel which, in turn, activates ERK and CaMK II signaling pathways, both of which are necessary for the consequent increase in synaptic strength

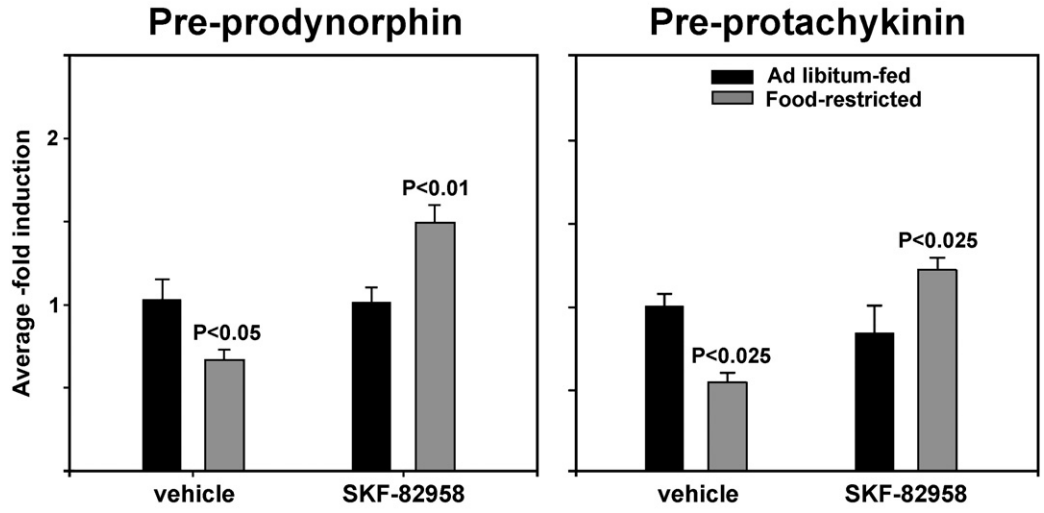

Fig. 9. Effects of i.c.v. injection of SKF-82958 (20 μg) on mRNA levels of neuropeptide genes in the NAc determined by real-time RT-PCR analysis. All data were normalized for levels of β-actin expression within the same sample and represent group means (±s.e.m.) of percentage induction over the control AL, vehicle-treated group. In vehicle-treated subjects, mRNA levels for both preprodynorphin and preprotachykinin were lower in FR than AL subjects. In SKF-82958-treated subjects, mRNA levels for both neuropeptides were higher in FR than in AL subjects (see text). This figure is adapted from one previously published [73] with the kind permission of Elsevier Science Ltd. (Copyright 2005).

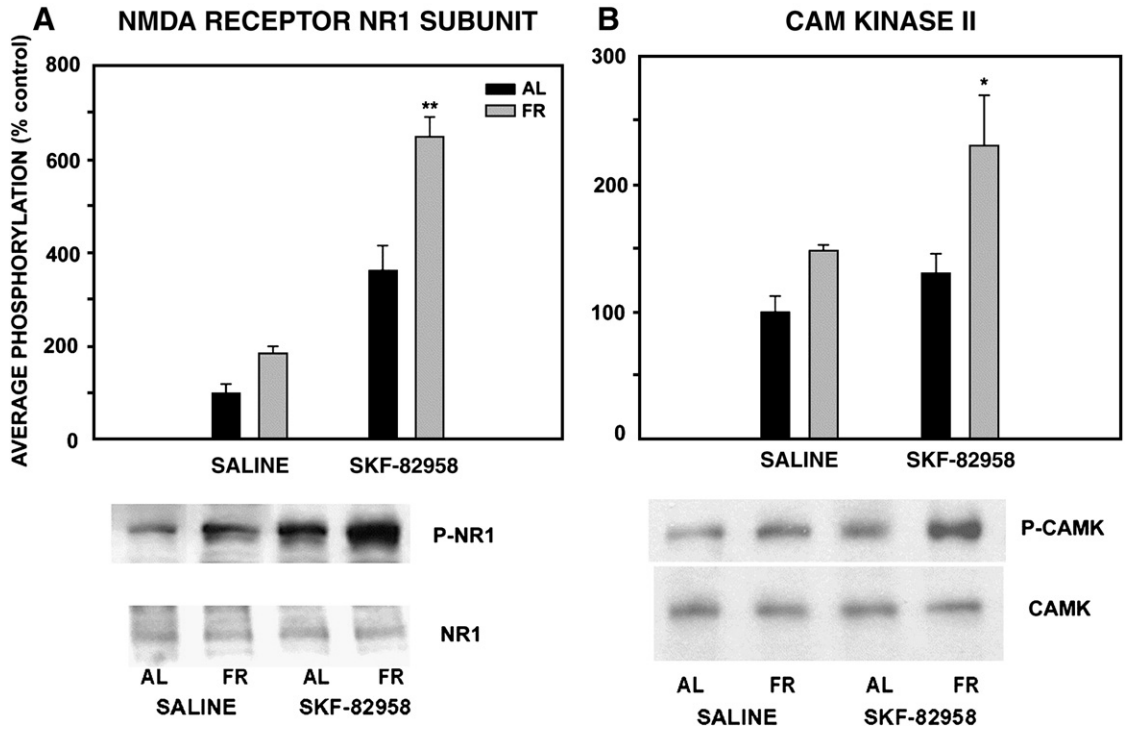

Fig. 10. Effects of SKF-82958 on NMDA receptor and CaM Kinase II activation in NAc. AL and FR rats received i.c.v. injections of SKF-82958 (20 μg) or saline vehicle prior to sacrifice. Lysates were immunoblotted with anti-phospho NR1 or anti-NR1 (1A) and anti-phospho-CaMK II or anti-CaMK II (1B) antibodies. Following densitometry, intensities of bands corresponding to phosphorylated proteins were divided by the intensities of the corresponding total protein bands to correct for small differences in protein loading. Results (mean±s.e.m.) are expressed in comparison to the normalized control, which was defined as the AL group injected with saline. Graphed results are displayed with representative immunoblots. FR increased the activation of NR1 and CaMK II by SKF-82958 but did not alter total NR1 or CaMK II (lower set of bands). This figure is reproduced from a previous publication [84] with the kind permission of Elsevier Science Ltd. (Copyright 2005).

[82,86,91,92]. During the last several years, evidence has accumulated to indicate that a similar mechanism is present in striatal neurons [93,94] and is likely to mediate goal-directed behavior, reward-related learning and the underlying neuroplastic changes [53,81,95,96]. The AMPA receptor GluR1 subunit, which is Ca^{2+} permeable, is trafficked to the synaptic membrane in an activity-dependent manner, and one mechanism of GluR1 trafficking, as occurs in LTP, involves NMDA receptor activation and downstream activation of ERK and CaMK II [82,86,91, 92,97–99]. Because AMPA receptors mediate fast excitatory transmission while NMDA receptors are the key to induction of various forms of synaptic plasticity [100], it is possible that increased synaptic insertion of GluR1 consequent to upregulated D-1/NMDA receptor-dependent cell signaling is involved in the enhanced behavioral responsiveness of FR subjects to drugs of abuse. On the other hand, long term depression (LTD) has also been demonstrated in striatal neurons and this response, which involves removal of GluR1 subunits from the membrane, also requires the NMDA receptor and consequent Ca^{2+} conductance [101]. In fact, results of electrophysiological [101] and biochemical [102] studies seem to suggest different conclusions as to whether increased or decreased AMPA receptor function in NAc mediates enhanced sensitivity to drugs of abuse. The direction of change in AMPA receptor function in sensitized subjects may depend on whether the neurons under investigation belong to ensembles dedicated to drug-seeking or competing forms of goal-directed behavior [16,22]. Importantly, plastic changes in this system are believed to play a key role in compulsive goal-directed behavior, including drug addiction [53,103–105].

4. Possible changes in DA synthesis and utilization

There is reason to consider whether the upregulated striatal cell signaling in response to D-1 DA receptor stimulation in FR rats represents a compensatory response to decreased physiological DA release. The decreased basal levels of preprodynorphin and preprotachykinin mRNA observed in NAc of FR relative to AL rats, could be reflective of a persistently lower level of D-1 DA receptor stimulation in these subjects (Fig. 9) [73]. Further, there is the microdialysis result indicating that under basal conditions, extracellular DA concentration in NAc of FR rats is lower than in AL rats [56]. Finally, it is of interest that in the extreme case of DA deficiency produced experimentally by intra-mesencephalic 6-OHDA injection, D-1 DA agonist-induced behavioral responses and striatal Fos-immunostaining and MAP kinase activation are similar to the changes observed in FR rats [71,72,106]. To evaluate whether FR is associated with altered DA synthetic activity, quantitative real-time RT-PCR and *in situ* hybridization were used to measure mRNA levels for tyrosine hydroxylase (TH) — the rate-limiting enzyme in DA biosynthesis, but no differences in TH transcription were detected between feeding groups in ventral tegmental area (VTA) or substantia nigra [107]. It should be noted, though, that in adolescent male rats subjected to a brief FR regimen, TH mRNA was elevated in VTA [108].

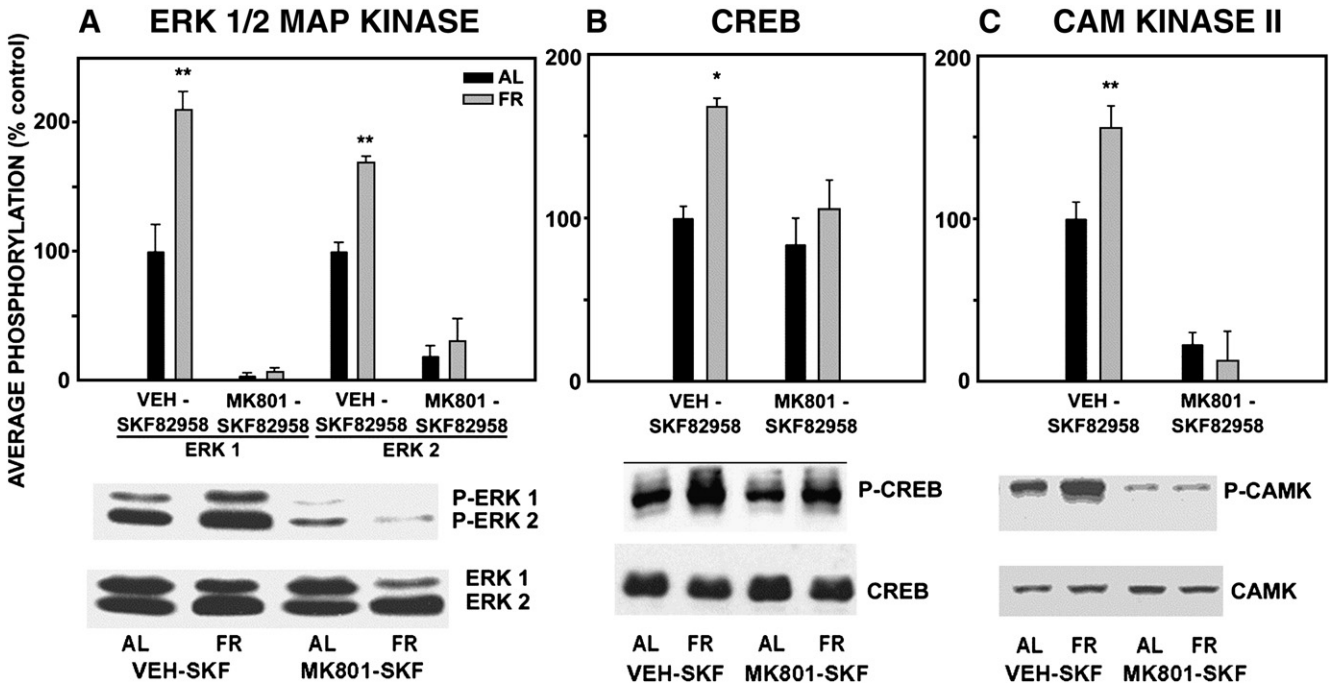

Fig. 11. Effects of MK-801 pretreatment (1.0 mg/kg, i.p., 30 min prior to i.c.v. injection of D-1 agonist) on SKF-82958-induced signaling in NAc of FR and AL rats. Lysates were immunoblotted with anti-phospho p44/42 ERK 1/2 MAP kinase or anti-p44/42 ERK 1/2 MAP kinase (2A), anti-phospho CREB or anti-CREB (2B), and anti-phospho CaMK II or anti-CaMK II antibodies (2C). The mean (±s.e.m.) ratios of phosphorylated to total protein levels, as determined by densitometric scanning, are expressed in comparison to the normalized control with corresponding representative immunoblots. Pretreatment with the NMDA antagonist suppressed activation of ERK 1/2 and CaMK II by SKF-82958 and eliminated the difference otherwise observed between feeding groups. Further, the NMDA antagonist selectively decreased activation of CREB by SKF-82958 in FR subjects, eliminating the difference between feeding groups. This figure is reproduced from a previous publication [84] with the kind permission of Elsevier Science Ltd. (Copyright 2005).

Despite the absence of change in TH mRNA in the midbrain of mature males in this laboratory, total TH protein concentrations were higher in NAc and CPu of FR relative to AL rats, suggesting a decrease in TH degradation and turnover. This may represent a mechanism for priming an increase in local DA synthetic capacity without transcriptional change. However, when tyrosine hydroxylation, reflected by DOPA accumulation following administration of an aromatic L-amino acid decarboxylase inhibitor, was measured in animals under resting conditions, decreases were observed in NAc and CPu of FR relative to AL rats [107]. Decreased DOPA synthesis, in the presence of increased levels of TH protein, may reflect the inhibitory effect of increased DA binding to TH protein or decreased concentrations of cofactor tetrahydrobiopterin [109,110]. Whatever the underlying explanation, decreased accumulation of DOPA indicates decreased DA synthesis and, particularly under the circumstance of decreased DA transporter function [62], implies decreased DA utilization. However, measures taken at a single time-point are probably inadequate to assess the alterations in DA neuronal function in FR subjects. Chronic FR may induce a variety of changes in DA dynamics, some of which are more durable than others and/or vary with environment and behavioral state. The limited evidence that exists, suggests that DA transmission and DA-dependent behavior of FR subjects describe a wider dynamic range than in controls, with conservation prevailing under basal conditions, and hyperresponsiveness to novelty and contexts/stimuli that signal opportunity for drive reduction [56–58,111–113]. Extension of this latter hyperresponsiveness to drugs of abuse is supported by microdialysis results [59,60] and the biochemical finding that *d*-amphetamine challenge decreases phosphorylation of TH at Ser-40 in NAc of FR but not of AL rats — a result indicative of increased feedback inhibition of DA synthesis and a possible consequence of increased extracellular DA concentration [107].

5. Potential endocrine contributions

A consistently observed characteristic of the enhancing effect of FR on drug reward sensitivity is that it reverses over a period of days/weeks in parallel with body weight recovery when ad libitum access to food is reinstated (e.g., Fig. 2) [42,47]. This raises the possibility of a role for one of the endocrine adiposity hormones – leptin or insulin – which circulate in plasma and cerebrospinal fluid (CSF) in proportion to body adipose mass [114,115], penetrate the blood–brain-barrier [116,117], and convey regulatory signals to the CNS, at least in part, via CSF circulation [118]. Hypoleptinemia is responsible for many adaptive responses to FR, and leptin administration reverses numerous behavioral and physiological responses that otherwise accompany persistent negative energy balance [37,115]. We therefore examined the effects of exogenous leptin administration in FR rats. When leptin or an agonist for the melanocortin 3/4 receptor – which mediates the downstream effects of hypothalamic leptin and insulin signaling [119,120] – was injected i.c.v. at doses that suppressed food intake in AL rats, the rewarding effect of *d*-amphetamine was "paradoxically" increased in both feeding groups [42,121]. When leptin was microinjected bilaterally in the

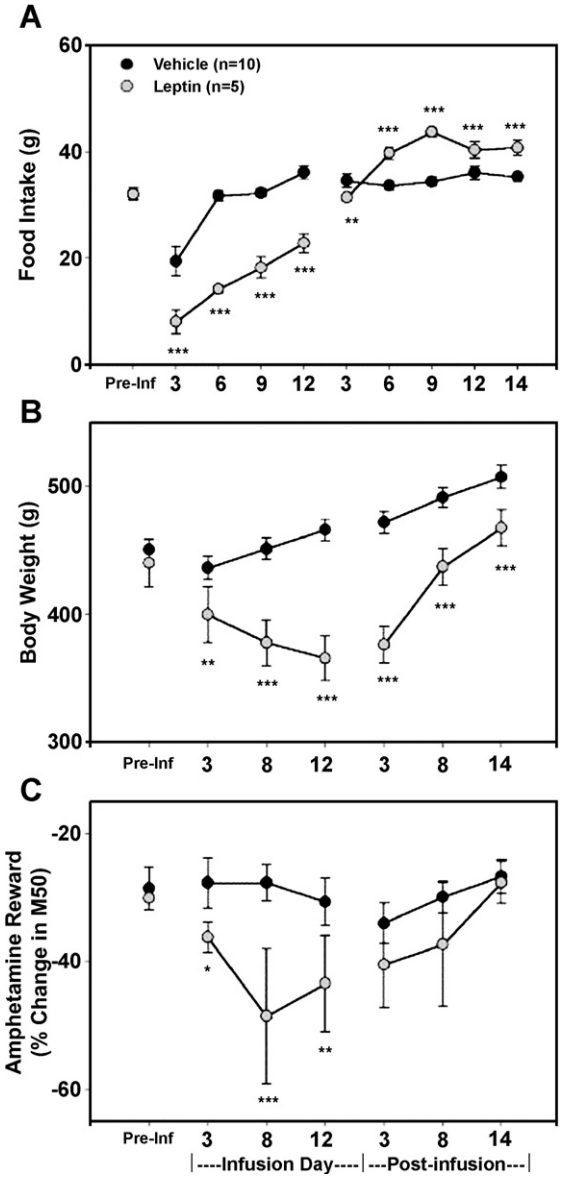

Fig. 12. Effects of chronic (12 day) i.c.v. leptin infusion on food intake, body weight and rewarding effect of *d*-amphetamine in AL subjects. (A) Effect of vehicle (0.5 μl/h; black circles) or leptin infusion (0.5 μg/0.5 μl/h; gray circles) on 24-h food intake averaged over consecutive 3-day periods (mean ± s.e.m.) in AL rats. (B) Body weight in grams (mean ± s.e.m.) of AL rats receiving vehicle (black circles) or leptin (gray circles) on each test day during and after infusion. (C) The threshold-lowering (i.e., rewarding) effect of *d*-amphetamine (0.50 mg/kg, i.p.) on lateral hypothalamic self-stimulation expressed as the percent change (mean ± s.e.m.) in threshold in the test immediately following *d*-amphetamine injection relative to the test immediately preceding *d*-amphetamine injection. Leptin decreased food intake, body weight, and increased the rewarding effect of *d*-amphetamine during the 12-day infusion period. During the two week post-infusion period, the previously leptin-treated group displayed rebound hyperphagia, recovery of body weight, and reversal of the enhanced rewarding effect of *d*-amphetamine. This figure is reproduced from a previous publication [122] with the kind permission of Elsevier Science Ltd. (Copyright 2006).

NAc or VTA, no change was observed in the rewarding effect of *d*-amphetamine [122]. Continuous 8–12 day i.c.v. leptin or melanocortin-agonist (MTII) infusion also failed to affect the rewarding and locomotor-activating effects of *d*-amphetamine in FR rats [122–124]. However, AL rats receiving the same chronic i.c.v. leptin infusion exhibited a sustained decrease in food intake, progressive body weight loss, and an enhanced sensitivity to the rewarding and locomotor-activating effects of *d*-amphetamine, which reversed in tandem with body weight recovery when leptin infusion was terminated (Fig. 12) [122,123]. Thus, hormone-induced appetite suppression produced the same type and time-course of change in behavioral sensitivity to *d*-amphetamine as experimenter-imposed FR. The possibility that these effects of chronic i.c.v. leptin infusion in AL rats reflect pharmacological effects of the exogenous hormone cannot be ruled out. However, these results raise the interesting, and potentially illuminating, possibility that rapid progressive body weight loss is sufficient to increase behavioral sensitivity to drugs of abuse, while the stress of deprivation and a persistently active hunger drive are not necessary. Should this prove to be the case, differential modulation of food and drug reward would be implied insofar as motivating and rewarding effects of even the most palatable foods are likely to be diminished in these leptin-treated subjects [125,126].

An additional concomitant of the decreased food intake and progressive weight loss observed in AL subjects receiving chronic i.c.v. leptin infusion was an elevation of plasma corticosterone concentration [122] comparable to that observed in FR rats [127]. An extensive literature indicates that behavioral sensitivity to psychostimulants is modulated by corticosterone and brain glucocorticoid receptors [e.g., 128–131]. Further, neuroplastic changes in excitatory synapses on DA neurons produced by psychostimulant drugs during the induction of behavioral sensitization are similarly produced by stress and mediated by glucocorticoid receptors [132]. In the particular case of FR, studies of glucocorticoid involvement have produced supportive, though complicated, results. Adrenalectomy with plasma corticosterone stabilized by subcutaneous implantation of a corticosterone pellet blocked the increased locomotor response to amphetamine challenge in rats following a brief, severe, regimen of FR (i.e., 20% body weight loss in 6–7 days) [133]. However, the blunting effect of this adrenalectomy treatment on morphine-induced locomotion was observed in both FR and AL rats. When morphine was injected into the VTA, however, the locomotor response was preferentially decreased in FR rats [134]. When a somewhat milder FR regimen was employed (10% body weight loss in 8 days) systemically administered cocaine produced an enhanced locomotor response in FR subjects, but the corticosteroid synthesis inhibitor, metyrapone, decreased the behavioral response in both feeding groups [135]. Using the synthesis inhibitor, ketoconazole, the increased heroin self-administration displayed by chronically FR rats was decreased in females but not males [136]. However, when studying the acquisition of cocaine self-administration behavior over the course of a 30-day period, ketoconazole pretreatment slowed the otherwise accelerated acquisition in male FR rats while having no effect in AL rats [25]. In the behavioral protocols used in this laboratory, neither metyrapone [42] nor the glucocorticoid receptor antagonist, RU-486 [Cabeza de Vaca and Carr, unpublished], attenuated the rewarding effect of *d*-amphetamine in FR rats. RU-486 was also ineffective against the wheel running behavior

uniquely displayed by FR rats given a discrete brief period of wheel access outside of the home cage [Cabeza de Vaca and Carr, unpublished]. If glucocorticoid receptors are preferentially involved in the induction rather than the expression [132] of sensitization by FR, and/or a persistent change in glucocorticoid receptor occupancy is required to alter the behavioral functions discussed here, then approaches other than acute administration of metyrapone and RU-486 during the expression phase will be necessary to identify the contribution of corticosterone.

6. Summary and conclusions

In summary, chronic FR increases central sensitivity to drugs of abuse, as evidenced in various assays of drug reward magnitude, locomotor activation, and immediate-early and neuropeptide gene expression in subcortical DA terminal fields. Upregulation of striatal cell signaling upon D-1 DA receptor stimulation represents one set of neuroadaptations associated with FR that may play a role in these effects. The NMDA receptor-dependent activation of CaMK II, ERK 1/2, and CREB have been implicated in neuroplasticity and reward-related learning, and may be adaptively upregulated in FR subjects to facilitate the learning of new associations and responses that increase the probability of food acquisition and ingestion. It is, however, possible that this mechanism can be subverted by drugs of abuse or certain patterns of palatable food intake, to foster maladaptive forms of goal-directed behavior, including drug addiction and binge eating. Endocrine responses to chronic FR may be involved in the triggering of CNS and behavioral changes in FR subjects, although limited testing of the candidacy of leptin provides no support for this adiposity hormone. Investigations of glucocorticoid involvement, in other laboratories, have provided some supportive results. However, studies focused on induction rather than expression, and treatments producing sustained, rather than transient, decreases in circulating hormone or receptor occupancy may be needed to assess involvement in behavioral responses described here. Among the many functional and mechanistic questions raised by the findings summarized, two of the most critical are whether upregulated striatal cell signaling is necessary for expression of increased behavioral sensitivity to acute drug challenge, and whether rapid body weight loss is sufficient to induce the behavioral and cellular effects of FR.

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