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Sweetened-Fat Intake Sensitizes Gamma-Aminobutyric Acid—Mediated Feeding Responses Elicited from the Nucleus Accumbens Shell

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Abstract

Background—There is much interest in exploring whether reward-driven feeding can produce druglike plasticity in the brain. The gamma-aminobutyric acid (GABA) system in the nucleus accumbens (Acb) shell, which modulates hypothalamic feeding systems, is well placed to “usurp” homeostatic control of feeding. Nevertheless, it is unknown whether feeding-induced neuroadaptations occur in this system.

Methods—Separate groups of ad libitum-maintained rats were exposed to daily bouts of sweetened-fat intake, predator stress, or intra-Acb shell infusions of either d-amphetamine (2 or 10 µg) or the µ-opioid agonist D-[Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO, 2.5 µg), then challenged with intra-Acb shell infusion of the GABA_A agonist, muscimol (10 ng).

Results—Exposure to sweetened fat robustly sensitized muscimol-induced feeding. Sensitization was present 1 week after cessation of the palatable feeding regimen but had abated by 2 weeks. Rats exposed to sweetened fat did not show an altered feeding response to food deprivation. Repeated intra-Acb shell infusions of DAMGO (2.5 µg) also sensitized intra-Acb shell muscimol-driven feeding. However, neither repeated intra-Acb shell d-amphetamine infusions (2 or 10 µg) nor intermittent exposure to an aversive stimulus (predator stress) altered sensitivity to muscimol.

Conclusions—Palatable feeding engenders hypersensitivity of Acb shell GABA responses; this effect may involve feeding-induced release of opioid peptides. Heightened arousal, aversive experiences, or increased catecholamine transmission alone are insufficient to produce the effect, and a hunger-induced feeding drive is insufficient to reveal the effect. These findings reveal a novel type of food-induced neuroadaptation within the Acb; possible implications for understanding crossover effects between food reward and drug reward are discussed.

Keywords

DAMGO; feeding behavior; GABA_A receptor; muscimol; opioid; sensitization

It is hypothesized that a major contributing factor to the current obesity “epidemic” is the prevalence of cheap, highly palatable, energy-dense foods that drive nonhomeostatic feeding behavior through their strongly rewarding properties (1–3). Because these foods engage the

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same central pathways implicated in addiction (4–6), there has been considerable interest in determining whether their intake engenders neuroplastic changes akin to those produced by drugs of abuse. The systems receiving the most attention in this regard are the dopamine and opioid systems in the nucleus accumbens (Acb). Several groups have shown that repeated exposure to palatable feeding, especially upon sugar- or fat-enriched foods, strongly alters neurotransmitter dynamics, receptor sensitivity, and gene expression within these systems and produces binge-like feeding patterns and other behavioral changes reminiscent of addiction-like processes (7–13).

Another key player in the neural control of appetitive behavior is the Acb-localized gamma-aminobutyric acid (GABA) system. Acute inhibition of Acb shell neurons with GABA agonists elicits a massive feeding response in satiated rats; this effect ranks among the most dramatic syndromes of drug-induced hyperphagia elicited from anywhere in the brain (14–19). This hyperphagia derives, in part, from the recruitment of peptide-coded hypothalamic systems that are involved in energy balance regulation (20–22). Furthermore, the anterior Acb shell is the only telencephalic site known to support GABA-induced facilitation of hedonic taste reactivity (23). The Acb shell has therefore been proposed as an essential node in the forebrain network that modulates downstream energy-balance systems in alignment with affective/motivational contingencies (24–26). A network node with these properties could therefore represent a crucial locus for palatable feeding-induced neuroplasticity; surprisingly, however, the Acb shell GABA system has not been studied in this regard.

Our goal in this study was to assess whether repeated experience with reward-driven, nonhomeostatic feeding engenders neuroadaptations in Acb shell GABA systems. We discovered that a modest regimen of intermittent sweetened-fat intake robustly sensitizes feeding responses elicited by direct stimulation of GABA_A receptors in the Acb shell. We investigated the behavioral and pharmacologic mechanisms underlying this effect, with emphasis on the possible involvement of local intra-Acb shell opiate and dopaminergic mechanisms.

Methods and Materials

Subjects

Male Sprague-Dawley rats (Harlan Laboratories, Madison, Wisconsin) weighing 300 to 325 g upon arrival were housed in pairs in clear cages with ad libitum access to food and water (except for certain experiments as described subsequently) in a light- and temperature-controlled vivarium. They were maintained under a 12-h light/dark cycle (lights on at 7:00 AM). All facilities and procedures were in accordance with the guidelines regarding animal use and care from the U.S. National Institutes of Health and were supervised and approved by the Institutional Animal Care and Use Committee of the University of Wisconsin.

Surgery and Placement Verification

Bilateral stainless steel guide cannulae aimed at the Acb shell (23-gauge) were implanted according to standard stereotaxic procedures [for details, see Baldo and Kelley (27)]. Coordinates of the infusion site (in millimeters from the bregma) were +3.2 (anteroposterior); +1.0 (lateromedial); –5.2 from skull surface (dorsoventral). Wire stylets were placed in the cannulae to prevent blockage, and rats recovered for up to 7 days before testing. At the end of each experiment, cannulae placements were determined by viewing Nissl-stained brain sections under light microscopy (for further details, see Supplement 1). Rats with incorrect cannulae placements were dropped from the statistical analysis; the group sizes given in this section represent the final group sizes after subjects with incorrect placements were omitted.

Drugs and Microinfusions

Stainless steel injectors (30-gauge) were lowered to extend 2.5 mm past the tip of the guide cannulae. Bilateral pressure injections were made using a microdrive pump. Drugs were infused at a rate of .32 μL per minute. The total duration of infusion was 93 sec, resulting in a total infusion volume of .5 μL per side. After infusions, injectors were left in place for 1 min to allow for diffusion of the injectate before replacement of stylets. Muscimol, D-[Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO), and d-amphetamine (AMPH) were all dissolved in .9% sterile saline.

Palatable Feeding Regimen

Rats were exposed to two 30-min sessions (a morning and afternoon session) per day for 5 consecutive days. These sessions took place in Plexiglas testing cages identical to the home cages, except with wire grid floors to allow for the easy collection of food spillage. During the morning session (11:00–11:30 AM), rats were offered either sweetened fat (experimental group; $n = 14$) or standard chow (control group; $n = 14$) and allowed to eat freely. The sweetened-fat was a Teklad experimental diet (TD 99200) consisting of shortening with 10% sucrose, with an energy density of 6.2 kcal/g (for further details, see Supplement 1). Water was available for both groups. They were then returned to their home cages, with food and water freely available. In the afternoon sessions (3:00–3:30 PM), rats were placed again in the testing cages, but both groups were given standard chow (and water). Thus, rats in the experimental group experienced both palatable food and standard chow in the testing environment. This was done to acclimate the experimental group to receiving chow in the testing cages, because chow was used in the second phase of the experiment (see “Low Dose Muscimol Challenge in the Testing Environment,” below). Intake in the testing cages was recorded each day. Standard chow (Teklad rodent laboratory diet) and water were available at all times in the home cages.

Stressor Exposure Regimen

This manipulation mimicked the 5-day palatable feeding schedule, except that rats in the experimental group ($n = 11$) received an aversive stimulus (predator stress), instead of palatable food, in the morning sessions. Each rat was placed daily into a protective metal grid cage (7 in $\times$ 8 in $\times$ 9 in) that was placed for 5 min inside the home cage of the ferret (a natural predator of rats). The protective cages allowed the animals to see, hear, and smell each other but prohibited physical contact. This level of exposure is known to significantly elevate plasma corticosterone levels and promote heightened arousal and vigilance that lasts for at least 30 min beyond the termination of the ferret exposure (28,29). Control rats ($n = 10$) were placed into identical small protective cages and moved to a novel, but neutral (i.e., no ferrets), room. Following 5-min ferret or neutral exposure, experimental and control rats were removed from the small cages and immediately placed in the standard Plexiglas testing cages (see “Palatable Feeding Regimen” for details) in a testing room different from either the ferret or neutral room, for a 30-min session (11:00–11:30 AM). Food (standard rat chow) and water were freely available. All rats were returned to their home cages after this session. To further mimic the palatable feeding schedule, all rats were then exposed to a second 30-min daily session (3:00–3:30 PM) in the same testing cages as their morning cages, but with no ferret (or neutral) exposure. Again, food and water were freely available for this afternoon session. Rats were returned to their home cages upon completion of testing.

Repeated AMPH Regimen

This manipulation mimicked the 5-day palatable feeding schedule, except that rats in the experimental group received daily intra-Acb shell infusions of AMPH, instead of palatable food, for their daily morning sessions. Intra-Acb shell infusions of AMPH (2 or 10 μg , $n =$

11 for each dose) or saline ($n = 20$) were given immediately before the rats were placed into the testing cages for their morning sessions (11:00–11:30 AM). Standard rat chow and water were freely available during this time, and intake was recorded. AMPH-induced hyperactivity was monitored by an experimenter blind to treatment, using a time-sampling behavior-observation procedure in which the number of occurrences of four behaviors (cage-crossing, rearing, directed sniffing, and grooming) was recorded in 20-sec time bins every 5 min for each rat. Rats from the predator stress experiment were reused for the 2- μ g AMPH group.

All rats received a second daily exposure to the testing cages (3:00–3:30 PM) with standard chow and water present but with no drug infusions. Rats were returned to their home cages upon completion of testing.

Low-Dose Muscimol Challenge in the Testing Environment

Following 5 days of exposure to the sweetened fat, predator stress, or repeated AMPH manipulations, rats received bilateral intra-Acb shell challenges with saline and muscimol (10 ng/.5 μ L per side) in the testing environment. Saline was given to all rats on the sixth day (i.e., 1 day after cessation of their respective 5-day treatment manipulations), and intra-Acb shell muscimol on the seventh day. On each of these days, rats received their intra-Acb shell infusions immediately before placement in the testing cages for their accustomed afternoon session (3:00–3:30 PM). No morning sessions were given on these days. Food (standard chow) and water were freely available. Intake was measured, and rats were returned to their home cages upon completion of testing. Chow was used for this phase of the experiment because all groups had previously received chow in the testing environment, thus eliminating the confound of food novelty. Furthermore, because baseline levels of chow intake were low, there was less of a chance of encountering ceiling effects for muscimol-induced hyperphagia.

A subset of the rats exposed to the palatable feeding regimen ($n = 10$ sweetened fat, $n = 10$ chow controls) received additional saline and muscimol infusions 7 days after the end of the sweetened-fat exposure protocol with no sweetened-fat exposure in between. A third saline/muscimol infusion sequence was given to these rats 14 days after the end of the protocol, again with no interim sweetened-fat exposure.

Note that the order of saline and muscimol infusions was not counterbalanced (i.e., saline always came first), so that any possible context or cue-induced conditioned feeding responses could be detected on the saline-challenge day without the interpretational confound of a preceding muscimol challenge. Also note also that for the 10- μ g AMPH group, an additional muscimol challenge (50 ng) was given on Day 8.

Food-Deprivation Challenge in the Testing Environment

Rats were subjected to the palatable feeding regimen for 5 days as described earlier ($n = 10$ for the sweetened-fat group, $n = 11$ for the chow control group). On the sixth day, all animals received a saline infusion and were tested in their accustomed afternoon session (3:00–3:30 PM) with standard chow and water available. No morning session was given. Next, all rats received a food-deprivation challenge in which food was removed from the home cages 18 hours before testing (i.e., on the evening of the saline challenge day). On the next day, these food-deprived rats were given intra-Acb shell saline infusions and placed in the testing cages (with standard chow and water present) at the afternoon testing time, with no morning session. Intake was measured, and rats were returned to their home cages upon completion of testing.

DAMGO/Muscimol Cross-Sensitization

We used a slightly different design for this experiment, because 2.5- μ g DAMGO causes sedation on the rats' first drug exposure; this sedation abates in approximately 30 to 45 min (whereupon rats begin to eat for ~90 min). Hence, we used a single 2-hour-long daily session with no afternoon session. Ad libitum-maintained rats were given four intra-Acb shell infusions (one infusion per day, every other day) of either sterile .9% saline ($n = 7$) or DAMGO (2.5 μ g/.5 μ L per side; $n = 6$). After infusion, rats were immediately placed in testing cages for 2 h (11:00 AM–1:00 PM) with access to standard chow and water. Forty-eight hours after the last of the repeated treatments, the subjects received an intra-Acb shell infusion of sterile saline and were placed in the testing cages for 2 hours with standard chow and water. Two days later, they were challenged with muscimol (10 ng/.5 μ L), again placed immediately after infusion into the testing cages for 2 hours with standard chow and water. On each testing day, intake was recorded, and rats were returned to their home cages immediately after the end of the testing session.

Statistical Analysis

Two-factor analyses of variance (treatment $\times$ day, or treatment history $\times$ drug challenge, as appropriate) with planned comparisons were used to assess differences between experimental manipulations (diet, drug treatment, stress) and respective controls. Alpha was set at $p < .05$. Analyses were conducted using StatView software (SAS Institute, Cary, North Carolina).

Results

Intermittent Bouts of Sweetened-Fat Intake Sensitize the Feeding Response Elicited by Intra-Acb Shell Muscimol

Intake of sweetened fat in the morning feeding sessions escalated over the course of the 5-day intermittent-access protocol [$F(4,52) = 13.3$; $p < .0001$; Figure 1A]. On the fifth day, mean sweetened-fat intake was 4.9 g, equivalent to 30.4 kcal, compared with the mean intake of 1.8 kcal of chow in the control group. Importantly, there were no overall differences in body weight between the sweetened-fat and chow groups over the course of the 5-day protocol [$F(1,26) = .3$; not significant (ns)], and no diet $\times$ day interaction on body weight [$F(4,104) = 1.2$; ns]. Hence, rats in the experimental group appeared to compensate for the increased caloric intake, likely by reducing their ad libitum chow intake in the home cages (i.e., the brief episodes of sweetened-fat exposure did not engender obesity-like effects). For the afternoon sessions, in which both groups were offered chow, there were no between-group differences in intake and no diet $\times$ day interaction (F s = .2–1.3; ns). Hence, the morning sweetened-fat exposure did not influence the low rate of feeding seen in the afternoon chow-intake sessions.

Upon completion of this intermittent-access protocol all rats were challenged with intra-Acb shell infusions of saline and muscimol (10 ng). Rats exposed to sweetened fat did not show an altered feeding response to saline challenge compared with chow-exposed controls. However, they did show a robust, highly significant sensitization to muscimol-induced food intake (diet $\times$ drug interaction [$F(1,26) = 13.6$, $p = .001$; Figure 2 for specific comparisons]. Water intake was unaffected. As shown in Figure 2, muscimol sensitization was still present 7 days after the sweetened-fat regimen [$F(1,18) = 9.3$; $p = .007$]; 14 days after exposure, however, the sensitized response had diminished [$F(1,14) = 1.6$; ns]. Lastly, rats exposed to the sweetened-fat regimen did not show an augmented feeding response to an 18-hour food-deprivation challenge compared with their chow-exposed counterparts [$F(1,19) = .004$, ns; Figure 2].

Cross-Sensitization Between μ -Opioid Receptor and GABA Receptor Stimulation in the Acb Shell

As shown in Figure 3, intra-Acb shell DAMGO engendered robust hyperphagia on each of the 4 injection days of the “repeated DAMGO” phase [$F(1,11) = 62.3$; $p < .0001$]. After these repeated treatments, we challenged the rats with saline and muscimol; for these challenges, analysis of variance yielded strong main effects of chronic-treatment history [$F(1,11) = 7.8$; $p = .018$] and drug challenge [$F(1,11) = 12.1$; $p = .005$], but no interaction [$F(1,11) = 1.4$; ns]. Nevertheless, planned comparisons between the DAMGO and saline groups for each of the challenge injections revealed that food intake in response to intra-Acb shell muscimol challenge was significantly higher in DAMGO-treated rats compared with saline-pretreated rats ($p < .05$) but that the response to a saline challenge did not differ between the groups.

Absence of Muscimol Hypersensitivity After Repeated, Intermittent Stress Exposure or Intra-Acb Shell AMPH Infusions

Two experiments were carried out to test the effects of predator exposure and repeated AMPH treatments on subsequent responsiveness to muscimol. First, rats underwent a 5-day intermittent predator exposure regimen followed by intra-Acb shell saline and muscimol (10 ng) challenges. As shown in Figure 4, this history of stressor exposure did not alter the feeding response to a subsequent muscimol challenge [$F(1,19) = 1.1$, ns]. Next, the same rats were subjected to a 5-day regimen of daily intra-Acb shell AMPH infusions (2 μ g). As expected, AMPH produced robust motor activation as reflected in “composite activity scores” of cage crossing, rearing, directed sniffing, and grooming (see Methods and Materials) compared with saline-treated rats [$F(1,22) = 53.9$; $p < .0001$; Figure 5A], indicating that the dose was clearly behaviorally active. Acute AMPH treatments did not, however, alter ingestive behavior [treatment $\times$ day interaction: $F(4,76) = .5$, ns; data not shown]. After completion of the repeated AMPH- or saline-treatment phase of the experiment, all rats were challenged with intra-Acb shell saline and muscimol. AMPH did not significantly alter sensitivity to muscimol-induced feeding (Figure 5B). There was a significant pretreatment $\times$ treatment effect [$F(1,19) = 3.6$; $p = .02$]; however, planned comparisons revealed that this interaction was mainly due to a large within-subjects difference in responses to saline versus muscimol challenges in the AMPH group ($p = .0009$). However, there was no significant difference between the saline and AMPH groups in response to the muscimol challenge ($p = .11$).

To further explore the effects of multiple AMPH infusions on muscimol sensitivity (considering that stressed rats were reused for the AMPH experiment and this previous stress experience could have modified their AMPH responses), a second experiment was conducted in a separate group of naive rats in which subjects underwent a 5-day regimen of intra-Acb shell infusions of a higher AMPH dose (10 μ g), followed by intra-Acb shell challenges with saline and two doses of muscimol (10 and 50 ng). Again, we observed a robust acute motor activation in response to the AMPH infusions [$F(1,22) = 83.7$; $p < .0001$; Figure 6], but no effects on feeding [$F(4,76) = 1.7$, ns]. When these rats were challenged with either 10-ng or 50-ng intra-Acb shell muscimol, they failed to show sensitized feeding responses [$F(2,38) = 1.4$; ns]. As a positive control, rats in the AMPH group were then exposed to the 5-day sweetened-fat regimen (and rats in the saline group to the chow regimen); all rats were then challenged with an intra-Acb shell infusion of 10-ng muscimol. We observed a sensitized muscimol feeding response in these rats after sweetened-fat exposure [$F(1,19) = 5.8$; $p = .027$; inset, Figure 6], demonstrating that the same rats that failed to show sensitization after repeated AMPH infusions were capable of developing and expressing muscimol-sensitization in response to sweetened-fat exposure.

Cannulae Placements

Figure 7 shows a schematic mapping of cannulae placements from all experiments in this study. As can be seen in the figure, the vast majority of placements (95%) fell within the anterior half of the medial Acb shell, including the far rostral sector. Five percent of placements fell just caudal to the midpoint of the anteroposterior extent of the shell, within the sector that yields appetitive responses but rostral to the zone that yields defensive-like behaviors (18). Placements within these zones were evenly represented in all experiments, and there were no systematic differences in behavioral or pharmacological effects due to placement variability in the anteroposterior axis.

Discussion

In this study, we demonstrate a novel type of feeding-induced adaptation in the brain. Intermittent bouts of sweetened-fat consumption robustly sensitized the feeding effect induced by a low-dose muscimol challenge in the Acb shell; the sensitized effect was roughly equivalent to that produced by a fivefold higher dose of muscimol in naive rats. This hypersensitivity did not appear to be the nonspecific consequence of generalized arousal or environmental diversification associated with the intermittent sweetened-fat exposure. Accordingly, repeated exposure to highly arousing stimuli (intermittent stressor exposure), even those with positive motivational valence (intra-Acb shell AMPH) (30–33), were not sufficient to sensitize muscimol-induced feeding. In contrast, intra-Acb shell DAMGO infusions, which elicited feeding during the sensitization-induction phase of the experiment, produced robust cross-sensitization to muscimol. Hence, a common property of sweetened-fat intake and μ -opioid-driven chow intake, apart from their enhancement of general arousal, is required for the induction of GABA sensitization. Implicitly this demonstrates that orosensory or postingestive properties specific to sugar or fat are not obligatory for the development of muscimol sensitization. Instead, the common inducing mechanism may be repeated μ -opioid signaling in the Acb shell, produced either by exogenous DAMGO administration or endogenous μ -opioid peptide release provoked by sweetened-fat gorging.

In this regard, it has been shown that stimulation of intra-Acb μ -opioid receptors at the level of the Acb produces opioid-sensitization and a conditioned feeding response to subsequent saline challenge (34). These effects are dopamine-independent (35), as are other Acb-localized, μ -opioid-mediated processes such as the enhancement of hedonic taste reactivity (30,36,37). In a general sense, the failure of repeated AMPH infusions to sensitize muscimol-induced feeding agrees with these findings; thus, opioid-GABA cross-sensitization may represent a type of dopamine-independent neuroadaptation in the Acb. Interestingly, we did not observe a conditioned feeding response to saline challenge in DAMGO-treated rats. Note, however, that induction of the opioid-conditioned feeding effect can be variable and require more than four repeated treatments (V. Bakshi, personal communication, June 2012). Regardless, these results indicate that a conditioned feeding effect (at least, one capable of being revealed by saline challenge) is not required for the expression of opioid-GABA cross-sensitization. Moreover, we never observed augmented feeding responses in sweetened-fat-exposed rats in the afternoon chow sessions, or in response to saline or hunger challenges, indicating some degree of specificity in the eliciting mechanism for the sensitized feeding response.

The neural mechanism underlying feeding behavior engendered by muscimol and other amino acid manipulations in the Acb shell appears to be the perturbation of the balance of AMPA-mediated excitatory and GABA-mediated inhibitory signaling onto medium-spiny neurons. When the net effect is a reduction in the activity of these neurons, either by GABA-mediated inhibition or by blockade of AMPA-type glutamate receptors, robust hyperphagia

is triggered (14,23,38,39). Hence, a parsimonious explanation for our results is that repeated activation of μ -opioid receptors (by exogenously administered DAMGO or by endogenous opioid peptide release elicited by sweetened-fat gorging) enacts either a direct change in GABA_A receptor sensitivity per se, or a more general change in the balance of excitatory/inhibitory transmission such that the threshold for GABA-mediated inhibition is easier to achieve. Repeated opioid agonist (morphine) treatment produces certain effects in this direction, such as upregulation GABA_A binding sites and muscimol-stimulated chloride uptake in synaptosomes (40), augmentation of GABA_A δ -subunit expression in the Acb shell (41), and internalization of the GluR1 subunit of AMPA receptors in the Acb shell (42). Any of these mechanisms (or their combination) at the level of the Acb shell could conceivably produce hypersensitivity to muscimol-induced neural inhibition. Nevertheless, other explanations are possible; for example, there may also be neuroadaptations within “output” nodes of the network through which Acb-shell-mediated feeding behavior is expressed (such as the lateral hypothalamus). Additional studies are needed to test this possibility.

Regarding the clinical relevance of these findings, an interesting possibility is that GABA hypersensitivity in the Acb shell develops in response to environmental contingencies that provoke intermittent, phasic elevations in μ -opioid signaling, such as repeated “binges” of palatable feeding. In this context, the GABA change could represent a feed-forward mechanism for further dysregulated appetitive behavior. Our results may also have implications for understanding “crossover” effects between food reward and certain drugs of abuse. One obvious candidate is alcohol (EtOH), the effects of which are modulated by both μ -opioid and GABA systems in the Acb (43–45). Interestingly, some studies have reported associations among food cravings, bingeing, and pathologic alcohol use in humans (46,47). In animal studies, either GABA or opioid receptor blockade in the Acb shell reduce EtOH intake [(48,49), but see Stratford and Wirtshafter (50)], and, strikingly, EtOH is self-administered directly into the Acb shell (51). Furthermore, a recent positron emission tomography study revealed that μ -opioid signaling in the Acb accompanies the intake of a sweetened alcoholic beverage (52). At the cellular level, it has been shown that Acb shell-localized GABA_A receptors containing the δ subunit modulate the behavioral effects of low-dose EtOH consumption (53); as mentioned previously, expression of the gene for this subunit is upregulated in the Acb shell by repeated μ -opioid receptor stimulation (41). Hence, it is possible that release of μ -opioid peptides by palatable-food “snacking” in the context of EtOH drinking or the consumption of sweetened EtOH beverages (such as those marketed to youthful drinkers) may engage rapidly developing, opioid-dependent neuroadaptations in Acb shell amino acid-coded circuits. This hypothesis, although speculative, leads to testable predictions regarding a possible context in which GABA sensitization in brain reward circuits of vulnerable individuals could enable palatable foods to serve as a “gateway drug” for the escalation of food binges and EtOH intake.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Intake of sweetened-fat or chow in the 5-day intermittent exposure protocol, in which one group of rats received daily 30-min sessions of sweetened-fat (the “sweet fat” group, $n = 14$) in the morning (**A**) and chow in the afternoon (**B**), and the other group ($n = 14$) received chow in both the morning and afternoon sessions (the “chow” group). Error bars depict one SEM. *** $p < .001$, different from sweet-fat intake on Day 1.

Figure 2.

Rats exposed to the 5-day sweetened-fat exposure protocol displayed robust hypersensitivity to a low dose intra-nucleus accumbens (Acb) shell muscimol challenge, which lasted 7 days but had begun to diminish by 14 days. “Sal” indicates an intra-Acb shell saline challenge to both groups ($n = 14$ for both groups), and “Food Dep” indicates an 18-hour food deprivation challenge to both groups (which did not produce a between-groups difference). Feeding sessions shown here were 30 min long. Error bars depict 1 SEM. $**p < .01$; $***p < .001$, different from respective “chow” group on the same day.

Figure 3.

Rats treated repeatedly with intra-nucleus accumbens (Acb) shell infusions of the μ -opioid agonist D-[Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO) showed cross-sensitization to a low-dose muscimol challenge. The first intra-Acb shell saline (Sal) challenge was given to both groups. Next, rats received either intra-Acb shell DAMGO ($n = 6$) or saline ($n = 7$), on Days 1 through 4. DAMGO produced the expected hyperphagia ($***p < .001$, different from the respective saline group on the same day). Both groups were then given intra-Acb shell challenges of saline and 10 ng muscimol (Musc); the muscimol response in rats with a DAMGO history was significantly elevated ($*p < .05$, different from the saline group on that day). Error bars depict 1 SEM.

Figure 4.

Rats exposed to intermittent, brief episodes of predator stress over 5 days (see Methods) did not exhibit any change in sensitivity to intra-nucleus accumbens (Acb) shell muscimol challenge. Group sizes were 11 rats for the ferret-stress group, 10 for the no-ferret group. Error bars depict 1 SEM.

Figure 5.

Repeated treatments with intra-nucleus accumbens (Acb) shell d-amphetamine (AMPH, 2 μ g) infusions did not engender hypersensitivity to the feeding effect of a low dose of intra-Acb shell muscimol. **(A)** Acute AMPH produced significant motor activation, reflected in Composite Activity Scores (see Methods and Materials). *** $p < .001$, main effect of AMPH ($n = 11$ rats) versus saline ($n = 10$). After completion of the 5-day AMPH regimen, both groups were challenged with saline and muscimol and tested in 30-min chow intake sessions; there were no significant between-groups differences **(B)**. Error bars depict 1 SEM.

Figure 6.

Repeated treatments with intra-nucleus accumbens (Acb) shell d-amphetamine (AMPH, 10 μ g) infusions did not engender hypersensitivity to the feeding effect of a low dose of intra-Acb shell muscimol (Musc). The overall design of this experiment was the same as shown in Figure 5. (A) Acute intra-Acb shell AMPH infusions provoked considerable hyperactivity ($***p < .001$, main effect of AMPH [$n = 11$ rats] versus saline [$n = 10$]). (B) After the AMPH regimen, no between-groups differences were seen in response to 10-ng or 50-ng intra-Acb shell muscimol challenges. Inset: After the muscimol challenges, rats in the AMPH group were given 5 days of exposure to the sweetened-fat protocol; rats in the saline group were given 5 days of the chow protocol. Both groups were then challenged with intra-Acb shell muscimol, revealing sensitization in the sweet-fat exposed rats ($*p < .05$). Error bars depict 1 SEM.

Figure 7.

Line drawings depicting injector placements in the nucleus accumbens shell from all experiments. Cross-hatched areas depict the zones into which 95% of placements fell; singly hatched areas depict placements for the remaining 5%. There were no systematic differences in placements among the experiments and no systematic differences in behavioral/ pharmacologic effects due to variability in the anteroposterior axis. Numbers depict distance in millimeters rostral to bregma. Reprinted from (54) with permission from Elsevier, copyright 1998.