

Review

Feed-forward mechanisms: Addiction-like behavioral and molecular adaptations in overeating

Johan Alsiö ^{a,b,c,*}, Pawel K. Olszewski ^{a,d,e}, Allen S. Levine ^d, Helgi B. Schiöth ^a

^a Department of Neuroscience, Functional Pharmacology, Uppsala University, Biomedical Center, Box 593, SE-751 24 Uppsala, Sweden

^b Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge CB23EB, UK

^c Department of Experimental Psychology, University of Cambridge, Cambridge CB23EB, UK

^d Minnesota Obesity Center, University of Minnesota, Saint Paul, MN 55108, USA

^e Department of Biological Sciences, University of Waikato, Hamilton, New Zealand

ARTICLE INFO

Article history:

Available online 28 January 2012

Keywords:

Obesity
Addiction
Craving
Plasticity
Dietary fat
Sugar

ABSTRACT

Food reward, not hunger, is the main driving force behind eating in the modern obesogenic environment. Palatable foods, generally calorie-dense and rich in sugar/fat, are thus readily overconsumed despite the resulting health consequences. Important advances have been made to explain mechanisms underlying excessive consumption as an immediate response to presentation of rewarding tastants. However, our understanding of long-term neural adaptations to food reward that oftentimes persist during even a prolonged absence of palatable food and contribute to the reinstatement of compulsive overeating of high-fat high-sugar diets, is much more limited. Here we discuss the evidence from animal and human studies for neural and molecular adaptations in both homeostatic and non-homeostatic appetite regulation that may underlie the formation of a “feed-forward” system, sensitive to palatable food and propelling the individual from a basic preference for palatable diets to food craving and compulsive, addiction-like eating behavior.

© 2012 Elsevier Inc. All rights reserved.

1. Introduction

1.1. With food reward being the main driving force for eating in the modern society, addiction-like overeating is a crucial factor in the obesity epidemic

Food reward, not hunger, has become the main driving force for eating in the modern society. We seek pleasure derived from consumption of rewarding foods that usually combine palatability and high energy density, even though overeating promotes body weight gain. Weight control programs aimed at reducing the intake of palatable food suffer from poor long-term compliance and food craving appears to be a critical factor underlying relapse to overeating. Importantly, craving for palatable calories has many similarities with drug craving observed in addiction, and obese as well as lean individuals often develop – as we will illustrate in the current review – addictive-like overeating behavior.

Drug addiction is a chronic relapsing disorder progressing from occasional use, through repeated drug taking, to loss of control over use and compulsive intake [215,235]. Neuroadaptations precipitated by drug use promote further drug seeking and drug

taking. Ultimately, if a drug addict attempts to abstain from drug use, drug craving ensues that may lead to a relapse long after the physical signs of withdrawal have subsided, making an addiction into an adverse condition, often lifelong, whose signs of manifestation need to be closely monitored on a virtually indefinite basis. Importantly, reward-driven overeating is oftentimes also characterized by repeated cycles of abstinence and apparent craving, as evidenced by the difficulties to adhere to healthy eating habits over extended periods of time. This makes excessive eating-driven obesity a chronic condition that is extremely difficult to overcome.

Drug addiction and food overconsumption share striking similarities at the physiological and behavioral level. Whereas the effect size differ by an order of magnitude, natural reinforcers and addictive drugs all activate the mesocorticolimbic dopamine (“reward”) system [21,22,57,112], and the pleasure experienced from both preferred food [193] and psychostimulants [62] correlates with the amount of dopamine release in the striatum. The role of reward processing in overeating is established and it implicates both limbic and cortical circuitry (see e.g., [29,108,125]). In fact, similar disturbances in these regions are observed in drug addicts and obese individuals: the binding to dopamine D₂ receptors is down-regulated in the striatum of cocaine, methamphetamine, and heroin addicts [224,219,218], as well as in the obese [225], whereas both obesity and drug addiction is associated with decreased cortical activity [76,221]. The causal relationship between

* Corresponding author at: Department of Experimental Psychology, University of Cambridge, Cambridge CB23EB, UK. Fax: +44 (0) 1223 333564.

E-mail address: ja476@cam.ac.uk (J. Alsiö).

such disturbances and reward-associated disorders remains unclear, but it is noteworthy that genetic variants related to dopamine signaling (e.g., the *TaqI* A A1 allele of the *DRD2* gene) have been associated with both drug addiction and obesity [144,201].

More evidence for interactions between overeating and drug taking stems from studies on experimental animals. In rodents, sucrose preference is associated with increased alcohol responsiveness [244], as well as with higher self-administration of both cocaine [77] and amphetamine [56]. Ghrelin, an orexigenic hormone released by the gut during fasting [141], activates the mesocorticolimbic dopamine system via receptors in the ventral tegmental area (VTA) and stimulates the intake of palatable food over standard chow [63], but injections of this hormone also increase alcohol consumption [95] and facilitate cocaine-induced conditioned place preference [54]. Accordingly, food restriction promotes self-administration of drugs of abuse [42], whereas injections of the adipocyte-derived anorexigenic hormone leptin hamper such self-administration [186].

The convergence of data from drug addiction and overeating is perhaps surprising, considering that whereas drugs of abuse act pharmacologically at molecular targets within the dopamine/opioid pathways (or subsidiary systems), palatable food primarily activates sensory systems, vagal afferents, and metabolic responses, through either anticipatory (sight, thought of food), oral (taste, texture, smell) or post-oral stimulation (including stomach distention, rise in plasma nutrients, and insulin release). However, these systems communicate with the reward system and they are individually capable of reinforcing food seeking and consumption of palatable or energy-dense food. That taste has an individual role in reinforcement is e.g., illustrated by the facts that naïve rats display high preference for the palatability of non-nutritive lipid tastants [181], and will fervently lever press to gain access to non-caloric sweeteners [38]. Likewise, sham-feeding rats (i.e., animals with a surgically implanted gastric fistula that is opened to drain imbibed liquids from the stomach) with intermittent access to sugar show a similar escalation of drinking (binge-like response) over time as do their controls (gastric fistula closed) [15]. Further, liquids containing either carbohydrates or lipids are reinforcing independently of taste, as they are capable of inducing conditioned taste preference and operant responding even when infused directly into the stomach [182,183]. Oral and postoral effects thus combine to reinforce food seeking in experimental animals, but stimuli paired with the delivery of palatable food also acquire incentive salience and maintain operant responding even in the absence of the primary reinforcer [66]. These learning mechanisms, however optimal throughout prehistory, all contribute to putting the modern man at risk for overeating and weight gain, with ensuing health problems. They are also at the core of drug addiction [66].

Repeated exposure to the reinforcing properties of drugs is a prerequisite for addiction to develop. As evidenced in animal studies, this occurs because, aside from transient effects on the mesolimbic dopamine system [57], drugs cause molecular adaptations throughout brain circuitry. These include changes in morphology [133] and synaptic plasticity [100,105], as well as altered signaling in glutamatergic [241,242], dopaminergic [35], cannabinoidergic [156], and serotonergic [236] systems, and a shift in the brain activity including the greater recruitment of dorsal regions of the striatum [65]. Neuropeptidergic adaptations are also reported, pertaining to e.g., opioids [231], orexins [109], and corticotropin-releasing hormone (CRH) [113]. Although the relative importance for these adaptations largely remains to be determined, they likely represent the sustained molecular changes underlying the behavioral outcome of repeated drug use and thus play important roles in the development of the compulsive drug-seeking and -taking behaviors characteristic for addiction.

From the parallels between drug taking in addicts and overeating of palatable food in obese individuals stems the question whether also palatable food, a reinforcer experienced daily, causes molecular adaptations that promote further consumption. Recent findings suggest that such plasticity occurs in addictive-like behavior also outside substance dependence [150]. If so, palatable diets in the modern environment may be noxious not only because of ensuing weight gain and its associated health risks, but also because adaptations have occurred in the neurobiology of the individual, driving the overeating of palatable food away from voluntary control and into compulsivity. We propose that such changes act in a “feed-forward” manner, both driving a positive feedback loop to enhance signals that stimulate further food intake, and triggering downstream events that block negative feedback. Accumulating data show that hedonic (non-homeostatic) components of eating forcefully override satiety signals (homeostatic regulation) [24,106,138]. However, less focus has been given to the plasticity of the neural circuitry underlying such palatability-driven overeating. Addictive-like eating behavior in rodents is therefore presented in Section 1.2. Further, in Section 2, we will review the evidence for sustained plasticity in response to energy-dense diets, which may contribute to the addictive-like eating behaviors observed in animals after extended access to palatable food, and to obesogenic eating behaviors in humans.

1.2. Hedonic deprivation precipitates food craving: insights from human and animal studies

1.2.1. The case for food craving in overeating and obesity

Food craving, a compelling desire to consume specific kinds of food, is a frequent phenomenon, experienced regularly by most individuals [86,233]. To some extent, it may serve a physiological function during, e.g., nutrient deficiency; but since the most commonly craved foods are sweet, salty, and fat-laden, palatability rather than nutritional value seems to be the main orexigenic factor [178,234,240]. Food culture and preferences also influence craving: American students reported chocolate, pizza, and chips as frequently craved food items [234], whereas sushi got high scores among Japanese students [111]. Because the craved foods tend to be more energy-dense than the habitual diet [72], it seems plausible that individuals that experience strong food craving may be at an increased risk of gaining weight, or be less likely to succeed in losing weight. This would be homologous to drug addiction, where drug craving is argued to promote relapse to drug taking during abstinence [118,168]. Indeed, craving for both high-fat (HF) and high-sugar (HS) foods has been positively associated with BMI [36], whereas binge eating in obese individuals [80] and in bulimics [230] has been strongly linked to craving. Brain imaging studies have identified neuroanatomical structures activated during food craving, including the caudal and medial orbitofrontal cortex, amygdala, striatum and midbrain [147,164,192]. Importantly, obese and lean subjects differ in brain activity during consumption and anticipation of palatable food [104,177,202,203]. For example, blunted activation was noted in the caudate nucleus of obese individuals during consumption of a palatable milkshake [202].

Food craving is thus heavily implicated in obesity, and it is important to determine which factors lead to such hedonic drive. During dieting, energy-dense foods are commonly excluded, though – perhaps counterintuitively – negative energy balance by itself does not seem to precipitate craving [86,87,210,233]; see however [162]. It is therefore noteworthy that stronger craving is reported specifically for food items that are currently excluded from the diet [86]. In agreement, dietary monotony has been shown to increase the number and intensity of reported craving episodes, and to increase consumption of the missing tastant when

the deprivation is discontinued [46,163,170]. Taken together, these results strongly suggest that craving is provoked by sensory deprivation (in effect, denying the pleasure of eating preferred or desired food), not by caloric restriction. Reduced energy consumption may reinforce search for preferred foods [162], but does not seem the main cause of it. This notion may have implications for diet regimens, since craving induced by hedonic deprivation may compromise adherence to weight control programs, but is also important when evaluating the validity of animal models of food craving.

1.2.2. Addictive-like overeating in animals maintained on palatable food

A plethora of evidence related to addictive-like overeating stems from rodent experiments (Table 1). Mice and rats readily acquire operant tasks reinforced by palatable foods and are highly motivated to obtain such tastants as measured by the maximum number of responses required to earn reinforcers on both fixed and progressive ratio schedules of self-administration [6,179]. Further, if provided with free access to high-fat high-sugar (HFHS) food in the home cage, rodents consume large amounts of energy, leading to weight gain particularly in animals prone to diet-induced obesity [122,167]. Notably, palatability promotes overfeeding both in the sated state [6] and during re-feeding after deprivation, when hunger signals are activated, highlighting the importance of hedonic contribution to eating regardless of the homeostatic state [152].

An important aspect of overeating in humans is the strong influence by the environment on everyday food choices. Thus, social cues, time of day, availability of food, and visual cues including size of packages, plates, and containers both influence the frequency and the size of meals (for a review, see [227]). Interestingly, questionnaire studies suggest that obese individuals are more responsive to environmental food cues [34], and less sensitive to internal cues, e.g., feeling full [229].

Although many cues stimulate food intake in general, i.e., regardless of pleasant taste [228], stimuli previously linked to palatable food are strong inducers of food craving and subsequent food consumption [87,162], suggesting a strong role for cues in addictive-like overeating. This phenomenon has been studied in the context of Pavlovian conditioning in rodents: even in sated rats, cues (e.g., a stimulus sound or an environmental context) stimulate feeding if they have been previously paired with the delivery of palatable food [166,232]. Importantly, in drug addiction, craving can occur months or even years after the last exposure to the drug, which is critical to the chronic nature of this disorder. Such craving can be induced by drug-associated cues, by small doses of the drug (priming), or by internal factors such as stress or anxiety

Table 1
Addictive-like eating behavior in animal models.

Extended access to HF/HS diets	Withdrawal from HF/HS diets
Escalation of intake	Self-restriction of standard chow
Bingeing	Sugar craving ↓
Reward sensitivity ↓	Cross-sensitisation to drugs
Operant response for sugar ↑	Anxiety-like behavior ↑
	Deprivation effect
	Compulsive food-seeking
	Cue-induced relapse to food seeking

Equivalent behaviors have been reported in animal models of addiction (e.g., bingeing on heroin in long-access paradigms, increased ethanol consumption after deprivation, cue-induced cocaine-seeking after extinction of an operant response). Behaviors listed are compiled from studies using different protocols for extended exposure to HF/HS diets, including both ad libitum access and scheduled access; liquid as well as solid tastants; cafeteria diets (composed of a number of HF and/or HS food items) and single-food diets. Time frame for withdrawal from palatable food likewise varies.

[93,190,222], which have also been shown to induce craving for palatable food [87]. Accordingly, food-paired cues potently induced reinstatement of food-seeking responses in mice (responding in the absence of food on a lever previously coupled to food delivery), even under conditions where reinstatement was not observed after stress or priming [131].

Overconsumption of calories during ad libitum access to palatable food occurs both in the acute and in the chronic phase, although animals typically overconsume most during the first several days when the food is still novel [116,167]. In contrast, animals on intermittent access to palatable foods dramatically increase their intake over time until reaching a plateau. If the animals have free access to regular chow and intermittent access to HFHS chow, intake of the palatable food quickly reaches binge-like levels (more than doubles), while chow intake is remarkably reduced [27]. Elevated consumption over time is observed also in drug self-administration studies [2,3], where such escalation of drug intake is interpreted as the development of tolerance to the effects of the drugs. Escalation of intake in the context of palatable tastants has been observed also when sweet liquids are presented [48,47]. Avena and co-workers developed a paradigm in which rats with intermittent access to sucrose or glucose solution (12 h daily) doubled their intake over a 10-day period, with a binge-like drinking pattern during the first hour of access each day [16,17,48,47]. It has been argued that such elevated intake of HS diets over time also reflects tolerance to the rewarding effects of sugar [18].

During extended access to palatable food, changes in the responsiveness of the reward system have been studied by testing the motivation for a range of reinforcers. Lever pressing for palatable food *per se* (sucrose reinforcers) was elevated during ad libitum availability of a HFHS diet in some studies [70,115] but not all [55,167]. Further, impaired acquisition of an operant response reinforced by cocaine was observed in rats maintained on saccharin-sweetened chow [41] and on a HF diet [239], suggestive of reduced sensitivity to psychostimulant reward. Conditioned place preference for amphetamine was likewise diminished [55], and amphetamine drinking was reduced by simultaneous access to either sucrose or fat [101]. These effects indicate that continuous (non-scheduled, non-deprived) long-term access to palatable food may promote further food seeking while the motivation for other reinforcers is attenuated. This concept is also substantiated by the results of an electrical intracranial self-stimulation (ICSS) experiment, showing that the sensitivity of the reward system was significantly reduced during exposure to palatable food: free access to a cafeteria-style HFHS diet increased thresholds needed to elicit self-stimulation [97]. Increased thresholds for ICSS were previously noted after cocaine and heroin self-administration [4,110]. Notably, after the cafeteria-diet exposure, the elevated thresholds were present even two weeks after the animals had been withdrawn from the HFHS diet and provided access only to standard chow [97].

1.2.3. Do rodents experience withdrawal from palatable food?

Several laboratories have investigated the effects of forced abstinence from palatable food on behavior in mice and rats, by first providing animals with long-term access to palatable food and subsequently replacing these diets with standard rodent chow. This is relevant because two of the hallmarks of substance dependence are the emergence of withdrawal symptoms upon the discontinuation of drug use (e.g., anxiety and negative mood states, but also physical symptoms such as tremor and tachycardia), and the aforementioned drug craving recurring even after the physical withdrawal symptoms have disappeared [note that whereas drug craving is not included in the clinical definition in the *Diagnostic and Statistical Manual for Mental Disorders IV*, it is acknowledged that drug craving is 'likely to be experienced by most (if not all)

individuals with Substance Dependence']. Although physical withdrawal during abstinence from palatable food seem unlikely (however, see below), psychological symptoms and craving suggest neural adaptations to the chronic exposure to food reward.

Firstly, when rats that have had extended access to palatable food are transferred back to standard chow, they eat very few calories and lose weight [85,97,121,167,205]. In other words, appetite for standard diets seems diminished by exposure to palatable food. Such rejection of standard chow is observed already after one week of access to palatable tastants [85]. Using a diet cycling paradigm, Cottone and colleagues were able to show that the reinforcing efficacy (i.e., break points on progressive ratio) of a low-sucrose diet gradually decreased in non-food restricted rats that had intermittent access to a palatable HS diet [52].

In contrast to the animals' self-restricted consumption of regular chow, appetitive behavior directed at palatable foods increases during forced abstinence from these diets. Avena et al. showed that after intermittent (12 h/day) access to glucose for 4 weeks, 2 weeks of forced abstinence significantly increased lever pressing for glucose when the animals regained access to this tastant [14]. This appetitive state during forced withdrawal from palatable food takes on compulsive characteristics, manifested as food seeking and excessive consumption despite short- and long-term negative consequences. After 4 weeks of ad libitum access to a HF diet, mice transferred to a regular diet withstood an aversive environment to receive HF food pellets whereas low fat diet-fed mice or mice with continuous access to a HF diet did not [205], suggesting that elevated motivation accompanies withdrawal. After extended access to a cafeteria diet, animals continued feeding on palatable food despite paired negative stimulation (an auditory cue previously associated with a foot shock) that reduced hedonic feeding in controls [97]. In an approach stemming from animal models of drug addiction [243], it was also shown that after extended access to a palatable chocolate diet, the majority of the animals continued to eat the food even after it was adulterated with quinine [85].

Further, Teegarden and Bale showed that animals withdrawn from a HF diet displayed elevated arousal and emotionality, and that this effect could be reversed by refeeding with HF food [205]. Anxiolytic effects of HF food have been previously reported [172] and, while not all data support this hypothesis [157], it might be speculated that consumption of palatable (especially HF) food during abstinence is stimulated by the drive to alleviate anxiety or stress through "self-medication" [53]. This seems plausible also in the light of the perhaps surprising findings from Colantuoni and colleagues, who used their intermittent access to sugar model to show that forced abstinence from glucose produces a state similar to opioid withdrawal in rats, with physical withdrawal signs including behaviors such as teeth chattering and forepaw tremor [48]. In addition, anxiety-like behavior in the elevated plus-maze test was increased during this forced-withdrawal state [16,48].

In stark contrast to the reduced responding for cocaine and amphetamine observed in rats with continuous access to palatable food, animals placed on forced abstinence from sucrose after a long-term intermittent access show enhanced responsiveness to alcohol and drugs of abuse [13,12,78]. In such animals, intake of alcohol is elevated [13], while both behavioral sensitisation induced by cocaine [78] and locomotor activity induced by amphetamine [12] are enhanced. In rats receiving daily sessions of access to sucrose pellets in a runway, locomotor activity during sessions increased over time, indicating behavioral sensitisation [117]. These animals display cross-sensitisation to other drugs: when injected with either cocaine or morphine in the absence of sucrose pellets, the rats show further increases in locomotor activity in the runway compared to controls.

Overall, behavioral data strongly indicate that adaptations in the processing of feeding reward occur during long-term exposure

to palatable food. These adaptations are manifested as addictive-like behavior during access to such diets (escalation of HF/HS diet consumption, binge eating, increased thresholds for ICSS) and, even more clearly so, during forced abstinence from palatability (food craving, compulsive food seeking, anxiety-like behavior). These findings from animal experiments mirror many of the observations from human studies.

2. Exposure to food reward leads to neuroadaptive changes in the brain

Since chronic exposure to feeding reward can provoke the significant behavioral changes in rodents described in the previous section, the question arises as to what molecular adaptations to palatable food underlie such behaviors. Due to the persistence of addictive-like behavior during (forced) abstinence from HF/HS diets, these neuroadaptations are expected to be chronic or sub-chronic in nature and only revert to normal levels after extended abstinence from palatability, if at all. In this section, we describe the evidence for palatable food-induced alterations in the feeding-related neural circuitry, promoting a positive feedback that manifests itself as elevated preference for and consumption of palatable food, ultimately precipitating food craving and - in consequence - increasing a likelihood of overconsumption. These effects include but are not limited to neuropeptidergic signaling within the hypothalamus and adaptations in the dopaminergic and opioid systems (Fig. 1). Below we present examples of neural systems whose altered activity upon exposure to rewarding tastants is thought to allow an occasional experience with palatable food to be transformed into a lifelong drive to seek feeding reward.

2.1. Mediators of hedonic feeding

In agreement with escalation of intake and altered responsiveness of the brain reward pathways, neuronal activation in reward-associated areas is affected by long-term exposure to palatable food. This is exemplified by the upregulation of the marker for neuronal activity, cFos, in a number of limbic forebrain regions (including the ventral striatum, bed nucleus of the stria terminalis, caudate putamen, and central amygdala) after three-week free access to a 10% sucrose solution in rats [171].

2.1.1. Endogenous opioids in palatability-induced feeding

Opioid peptides (e.g., enkephalin and dynorphin) and the opioid mu, delta, and kappa receptors (MOR; DOR; KOR) have been strongly linked to the hedonic aspects of feeding (for a review, see [155]). Opioid antagonists such as naloxone and naltrexone reduce feeding in food-restricted rats mainly when palatable food is provided [73,124,238] and lowers the preference for sweetened solutions in human volunteers [67]. Injections of opioid agonists (e.g., morphine or the MOR-selective agonist D-Ala2-N-Me-Phe4-Glycol5-enkephalin; DAMGO) accordingly stimulate the intake of food items that are preferred by individual animals (i.e., intake of dietary fat is promoted in fat-preferrers and carbohydrate consumption is elevated in carbohydrate-preferrers) in food-choice paradigms [64,79], whereas naloxone reduces such preference [74]. In agreement with a significant role for opioids in non-calorie driven appetite, acceptance and preference for saccharin, the non-caloric sweetener, is attenuated by naloxone and genetic deficiencies in the MOR [123,126,212,245].

Opioid peptides and receptors are expressed throughout the brain: in the brainstem, subregions of the hypothalamus, ventral tegmental area (VTA), and within different striatal compartments. At many sites associated with food intake control, opioid receptor antagonism reduces feeding; these include the arcuate (ARC),

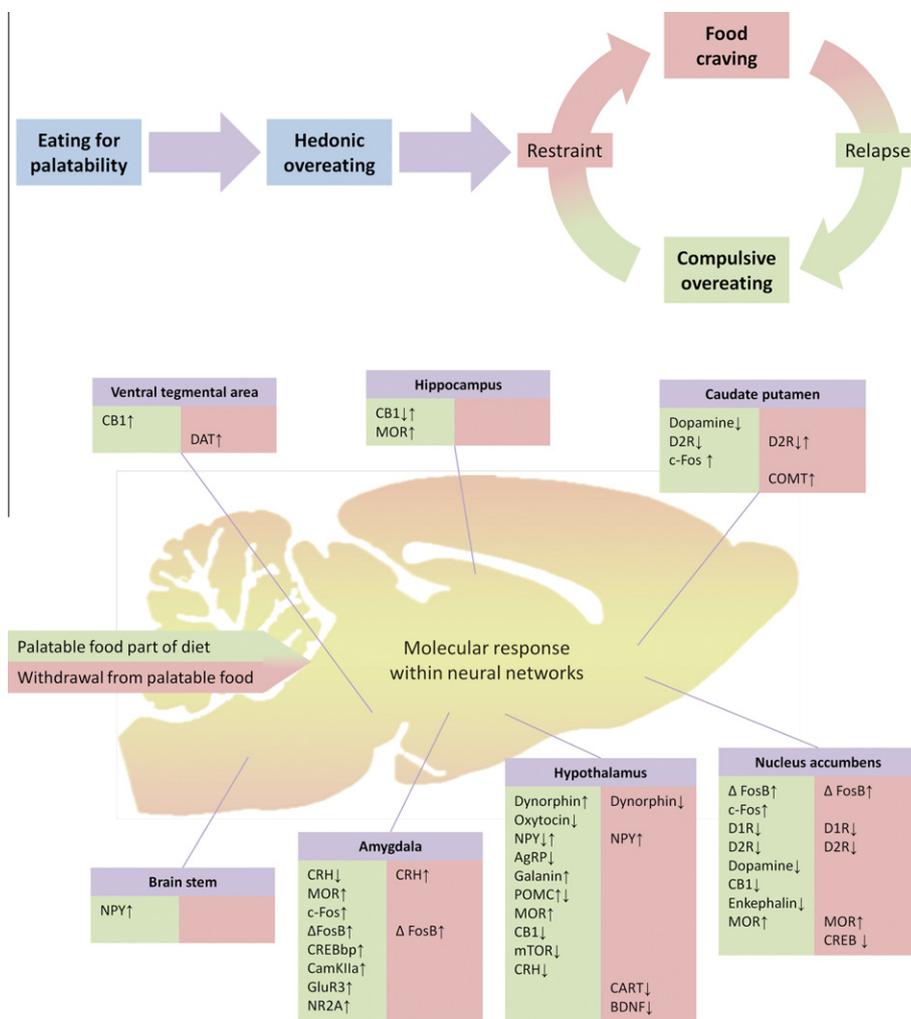


Fig. 1. Motivational and molecular adaptations in overeating. TOP: Overeating modeled as an addiction-like motivational progression from palatability-driven feeding to food craving and compulsive eating (i.e. overeating in spite of both negative consequences and efforts to reduce the intake of preferred, palatable food). The loop between dietary restraint and relapse to compulsive eating is characterized by loss of control over food intake. BOTTOM: signaling molecules implicated in food reward, hunger and satiety contribute to the positive feedback loop that drives eating behavior from a pleasurable experience to craving and compulsivity. AgRP, agouti-related peptide; BDNF, brain-derived neurotrophic factor; CamKII α , Ca²⁺/calmodulin-dependent protein kinase alpha; CART, cocaine- and amphetamine-regulated transcript; CB₁, type 1 cannabinoid receptor; COMT, catechol-O-methyl transferase; CREB, cAMP response element-binding protein; CREBbp, CREB binding protein; CRH, corticotropin-releasing hormone; DAT, dopamine transporter; D1R and D2R, types 1 and 2 dopamine receptor; GluR3, glutamate receptor 3; MOR, mu opioid receptor; mTOR, mammalian target of rapamycin; NR2a, NMDA receptor 2A; NPY, neuropeptide Y; POMC, proopiomelanocortin. ↑ denotes higher levels or activity; ↓ denotes reduced activity; ↑↓ denotes that both up-regulated and down-regulated activity have been reported.

paraventricular (PVN), and lateral hypothalamic nuclei, nucleus accumbens (Acb) shell (AcbSh), VTA, amygdala [75,142]. In the VTA and AcbSh, opioid receptors are present on GABAergic neurons, tonically inhibiting dopamine signaling [98]. MOR and DOR agonists injected locally into the VTA or AcbSh release dopamine in the AcbSh and increase hedonic feeding, while KOR agonists decrease AcbSh dopamine release and have no effect on food intake [37,58,128,145,146,198,199,249,247,246].

One of the specific roles for opioids in overeating seems to be in mediating the hedonic impact of, that is pleasure derived from, palatable food. Peripheral morphine injections enhance positive taste reactivity (tongue protrusions and licking the paws) elicited by sucrose in rats [158] and these effects are replicated when morphine or DAMGO are injected into specific anatomical locales within the AcbSh [159,160,194]. Injections into adjacent parts of the AcbSh promote food intake but do not affect taste reactivity [160].

Since opioids preferentially stimulate intake of food that is palatable, it was suggested that these peptides have a role also in chronic overfeeding. Indeed, a substantial body of evidence

indicates that exposure to palatable food changes the activity of opioidergic pathways. In the hypothalamus, prodynorphin mRNA levels were elevated in the ARC after 1-week ad libitum access to a HFHS diet; this effect was accompanied by higher levels of dynorphin A1-17 in the PVN [237]. After extended access to liquid and solid HFHS diets, with subsequent withdrawal to regular chow for three weeks, prodynorphin gene expression was decreased both in the ARC and ventromedial hypothalamus [136]. Further, MOR expression in a number of brain regions including the ARC was increased in HF diet-fed animals [19,195]. Additional effects have been observed in paradigms where palatable food was provided intermittently. MOR binding in several brain areas (AcbSh, cingulate cortex, hippocampus and locus coeruleus) was increased after a 30-day intermittent sugar exposure [47]. Rats both prone and resistant to diet-induced obesity displayed elevated gene expression of MOR in the Acb two weeks into forced abstinence from a HFHS diet [7]. Enkephalin expression in the Acb was decreased in animals on intermittent access to either sucrose [200] or a HFHS liquid diet [107]. It has been speculated that

downregulation of enkephalin causes a compensatory increase in MOR presentation [17]. Accordingly, long-term overeating was blocked by repeated infusions of a MOR antagonist in the AcbSh or core in rats [120].

Because chronic exposure to palatable food is presumed to repeatedly release endogenous opioids, it is interesting to note that upregulation of MOR binding [217] and downregulation of striatal enkephalin [211] is observed also after opiate infusions. To test the hypothesis that endogenous opioids are crucial for the behaviors observed during forced abstinence from palatable food, Colantuoni and colleagues administered naloxone to rats after long-term intermittent glucose access; it precipitated the same behavioral signs of withdrawal (e.g., teeth chattering and anxiety-like behavior) as did food deprivation [48]. Since these behaviors were not present in the reference groups (intermittent access to chow or ad libitum access to either chow or sucrose), the data suggest that intermittent access to sugar causes a dependent-like state to endogenous opioids.

2.1.2. Dopaminergic adaptations after extended access to palatable food

The mesocorticolimbic dopamine system is implicated in both obesity and drug addiction by virtue of its strong connections to food and drug reward [225,220]. Animal experiments show that dopamine is released in the striatum during intake of novel food items [21], but also if the food provided is palatable [174] or delivered during negative energy balance [22]. Further, dopamine release also occurs in response to cues (conditioned stimuli) predictive of food delivery [21,180]. Dopamine is suggested to encode the incentive properties of food [28]; the basis for this notion is that depletion of dopamine or blockade of dopamine receptors do not diminish pleasurable responses to palatable foods in animals or humans [28]. Mutant mice with elevated extracellular dopamine levels accordingly had higher motivation for sucrose in a runway task, while no differences were observed with regard to positive taste reactions [161]. This contrasts somewhat with data from brain imaging studies in humans, which show that striatal dopamine release in response to palatable food is proportional to the pleasure associated with eating that food [193].

Reduced striatal dopamine D₂ receptor levels have been observed in obese humans [225], which is strikingly similar to the findings from drug addicts [224,219,218]. Functionally, obese subjects also display blunted striatal response to palatable food [202]. Importantly, Stice and colleagues showed in a longitudinal study that such impaired striatal responsiveness develops as individuals gain weight [204], forcefully indicating the plasticity of the human reward system to metabolic/dietary challenges. In experimental animals, dopamine signaling is likewise attenuated after long-term access to palatable diets with or without concurrent obesity. Dopamine turnover in the Acb was decreased after both ad libitum and limited access to a HF diet [55]. Dopamine levels in the striatum were reduced after long-term (15-week) access to a cafeteria diet in rats [71], as measured by microdialysis with or without amphetamine injections to stimulate dopamine release. In coronal slice preparations, electrically induced dopamine release was attenuated in the diet-induced obese animals from both the Acb and the dorsal striatum [71]. Moreover, reduced D₂ receptor levels in the striatum of obese animals or after long-term access to HFHS diets in non-obese rats have been observed in some studies [82,83,97], although contrasting data also exist [92,196]. We showed that dopamine D₁ and D₂ receptors both were down-regulated in the Acb after 5-week intermittent access to a HFHS diet [7]. Also, we observed down-regulated D₁ receptor expression in the Acb in obesity-prone rats that were transferred from the HFHS diet to regular chow; these forced-abstinence rats furthermore presented elevated mRNA expression of COMT in the caudate

putamen and of dopamine transporter in the VTA [7]. Notably, Lenti virus-mediated knock-down of D₂ receptors in the dorsal striatum had no effect on food intake in the home cage or on weight-gain over time, but significantly affected compulsive intake of palatable food; i.e., knock-down rats continued to consume palatable food even in the presence of aversive stimuli, while sham-injected controls reduced food intake under such conditions [97]. The impaired dopamine activity in HFHS-treated animals has been suggested to cause a compensatory overconsumption of palatable food and motivation for feeding reward. This view is consistent with the fact that, in such animals, palatable food releases dopamine in the Acb while regular chow does not [71].

2.1.3. The endocannabinoids affect food intake at multiple levels

The type 1 cannabinoid receptor (CB₁) and its endogenous ligands (endocannabinoids such as anandamide) have emerged more recently as important players in hedonic aspects of feeding, although such a role had been expected based on the orexigenic effects associated with marijuana. Such appetite typically favors intake of palatable food and stems from CB₁ activation in a number of appetite-related sites including the hypothalamus, brainstem and striatum [25,60,173,187]. Whereas CB₁ receptors act presynaptically to inhibit both excitatory and inhibitory neurons, the orexigenic effects have been linked to the inhibition of glutamatergic input in the ventral striatum [25]. The CB₁ antagonist rimonabant accordingly reduces food intake and, hence, body weight in experimental animals [209], but it should be noted that it also affects body weight by acting on lipolysis and energy expenditure [94] and that the peripheral endocannabinoid system is affected in obesity [32]. Nevertheless, the anorexigenic effects seem stronger when palatable HS diets are offered [11]. Further, CB₁ receptor knock-out mice are lean compared to wild type littermates and do not develop obesity or leptin resistance on a HF diet [175]. In humans treated with rimonabant, food reward-induced neural activation is blunted in both striatal and orbitofrontal regions [90]. Such effects on the reward system are arguably associated both with the drug's efficacy in anti-obesity treatment and with its negative effects on mood [44].

As with the opioid system and dopamine pathways, alterations are observed in cannabinoidergic tone in reward areas after extended access to palatable food. After free access to palatable food for 10 weeks, CB₁ receptor binding in the Acb, hippocampus, and entopeduncular nucleus was inversely correlated to the amount of palatable food consumed and to weight gain [84]. Accordingly, CB₁ receptor binding was decreased in these areas in these rats compared to chow-fed controls [84]. In mice, diet-induced obesity was associated with elevated hippocampal levels of endocannabinoids and CB₁ receptor binding [132]. Also, after 20 weeks of HF diet exposure, CB₁ binding was elevated in the midbrain of mice, both in the VTA and in the substantia nigra [197]; a shorter exposure (3 weeks) caused decreased CB₁ binding in the hypothalamus [197]. Cannabinoidergic activity in the hypothalamus is directly regulated by leptin levels: leptin injections reduce hypothalamic levels of endocannabinoids whereas leptin-deficient strains display elevated endocannabinoid levels in the hypothalamus [59].

2.1.4. Downstream targets in food-reward-associated molecular adaptations

Several intracellular pathways that are activated by dopamine, opioid peptides and endocannabinoids and that are tied to overeating have been identified. Ulrich-Lai and colleagues exposed rats to a 2-week intermittent sucrose exposure (4 mL of 30% sucrose solution twice daily) and investigated gene expression in the amygdala using microarrays [214]. By performing functional clustering analysis of the genes significantly changed by their sucrose-drinking paradigm, they showed that calcium signaling pathways, as well

as genes related to synaptic long term potentiation, were affected in the amygdala of these rats (e.g., cAMP response element-binding protein (CREB) binding protein (CREBbp), Ca^{2+} /calmodulin-dependent protein kinase II α (CamKII α), and glutamatergic receptors including GluR3 and NR2A).

In the context of reward processing, one of the most studied transcription factors is Δ FosB, a remarkably stable protein that is found in high levels in the ventral and dorsal striatum under basal conditions, but that may be further induced by stress, dopamine denervation and pharmacological treatments [31,135]. Dopamine D₁ receptor stimulation is a strong contributor to Δ FosB induction [248]. Downstream targets of Δ FosB include substance P, dynorphin, GluR2, and NR1A [31,135]. Δ FosB is also upregulated in reward-associated regions including the Acb and amygdala after chronic drug exposure in rats, and thus may have an intimate association with substance dependence [143,165]. However, extended sucrose [45,223] or dietary fat [205] exposure also increased Δ FosB protein levels in the Acb and amygdala. Importantly, these elevated Δ FosB levels were observed even three weeks after the discontinuation of sucrose exposure [45]. In fact, rats fed a HF diet in early life (3 weeks old) display elevated Acb Δ FosB levels in adulthood (3 months old), concomitant with elevated HF diet preference [207].

From these findings stems the question which are the functional implications of elevated Δ FosB. Studies aimed at investigating this have employed genetic approaches including knock-in techniques and targeted viral delivery. Mice overexpressing Δ FosB in the striatum display elevated motivation for cocaine [49]. Mirroring the effects in models of addiction, experimenter-induced overexpression of Δ FosB in the striatum stimulates operant responding for both HS [149,223] and HF rewards [216]. Interestingly, high Acb expression levels of Δ FosB is associated with elevated preference for HF diets [207], but long-term exposure to HF diets normalize Δ FosB overexpression [206]. Plausible downstream targets of Δ FosB include dynorphin and the glutamate AMPA receptor subtype GluR2 [143].

Another transcription factor linked to drug addiction is CREB, which is expressed in all types of neurons and affects transcription by binding to cAMP response elements present on a large number of activity-dependent genes [40]. The main functions seem to be to convey behavioral and neuronal plasticity [26]; for instance, memory function in rodents has been shown to be impaired by CREB inactivation [33] and improved by CREB overexpression [99]. Like Δ FosB, CREB affects expression of genes relevant to reward and addiction, including dynorphin, CRH, and BDNF [40,39,134]. However, overexpression of CREB is associated with reduced responsiveness to cocaine [39]. Indeed, it seems like Δ FosB and CREB have opposing roles, as Δ FosB-overexpressing mice have reduced CREB levels in the striatum [206]. In contrast to Δ FosB, phosphorylated CREB is thus decreased in the ventral striatum after extended exposure to palatable food [205], whereas CREB inactivation in the striatum increases preference for sucrose and CREB overexpression decreases preference [20]. Taken together, both Δ FosB and CREB appear to play important roles in the propagation of overeating palatable food by affecting both preference and motivation for HS and HF diets and by doing so long after the exposure to such diets has been discontinued.

2.2. Interaction of hedonic and homeostatic pathways

Initial hypotheses on the neurophysiology of feeding reward focused on very select molecules (opioids, dopamine and, more recently, cannabinoids) acting within the highly specialized brain network dubbed the “reward system”. Likewise, “hunger” and “satiety” centers were described within the hypothalamus and brainstem, and signals within these structures were identified, including the first-order neurons (receiving input from circulating

hormones and nutrients) of the ARC, containing either neuropeptide Y (NPY)/agouti-related peptide (AgRP), or cocaine- and amphetamine-regulated transcript (CART)/proopiomelanocortin (POMC). Whereas the functions of these systems are often divided into non-homeostatic and homeostatic food intake regulation, it is established that reciprocal and functional interactions exist between the reward molecules and neuropeptidergic systems responsible for the regulation of calorie intake. This picture has been completed with the cognitive “top-down” control from prefrontal areas and input from both limbic and memory systems. In agreement with this integrative view of appetite regulation, receptors for the anorexigenic hormone leptin are present throughout the hypothalamus and brainstem nuclei, but also expressed and functional in the hippocampus and on dopamine neurons in the ventral tegmental area [89,102,185]. Likewise, ghrelin infusions directly into the VTA and nucleus accumbens increased food intake in rats [191]. In agreement with such neural interplay, leptin and ghrelin injections alter brain activity in striatal as well as cortical structures in humans [68,129]. In fact, the expression patterns of many genes classically associated with hunger, satiety, or reward display a high degree of overlap [151]. The neural circuits thus implicated in appetite regulation have been the subject of many excellent reviews [1,30,108].

2.2.1. Increased orexigenic drive

One important set of mechanisms strengthening palatability-driven hyperphagia is that the “classical” calorie intake regulators may in fact participate in shaping a response to palatable tastants by affecting preferences for macronutrients and flavors. This would explain why we are “hungry” for palatable foods despite not needing calories to replenish energy stores, why – when a choice of palatable foods is offered – we feel particularly hungry for tastants of specific macronutrient characteristics (fat, sugar, protein), and finally why satiety can be macronutrient- and flavor-specific too (e.g., we crave sugary food despite having reached fat-specific satiety after finishing a high-fat meal).

It has been shown that NPY preferentially stimulates intake of carbohydrates or sweet solutions [127,140], while HF diet consumption is stimulated by AgRP [81] and ghrelin [188]. During initial access to HFHS diets, elevated leptin levels inhibit NPY/AgRP neurons in the ARC while stimulating anorexigenic POMC/CART neurons [169]. Similarly, stimulatory input to orexin neurons in the lateral hypothalamus is inhibited by leptin [91]. Accordingly, NPY and AgRP levels were downregulated in the hypothalamus after 2 days of a HF diet in mice, but returned to baseline after 1 week [250]. POMC expression was elevated after 2 weeks in the same study, but the animals still overconsumed HF food. In rats provided access to a free-choice HFHS diet for 7 days, NPY levels were upregulated while POMC levels were down [116]. NPY gene expression was also increased in the brainstem after two weeks of scheduled HS exposure [152]. Such data suggest that, while the immediate response to overconsumption of palatable diets is anorexigenic in nature and counteracts palatability-induced hyperphagia, the neurobiological response is blunted or even reversed over time. In agreement with this, animals initially display a strong hyperphagic response during access to a given palatable diet, but also maintain elevated consumption levels long-term. Further, as described above, animals transferred from HF/HS diets to standard chow display elevated appetite when the palatable diet is reintroduced. In line with this, Archer and colleagues found elevated mRNA levels of NPY in the hypothalamus of rats transferred from high-energy diets to standard chow [10]. These adaptations may promote overconsumption if the palatable diets are offered anew.

Another neuropeptide associated with HF diet preference and fat consumption is the orexigen galanin, which is expressed in multiple hypothalamic sites including the PVN and ARC. While

expression of this peptide seems unaffected by caloric deprivation [96], food intake in sated rats is stimulated by galanin injections throughout the hypothalamus, in particular into the PVN [114]. These effects are stronger if HF diets are offered [148,208] and, accordingly, fat ingestion is reduced by intra-PVN injections of antisense galanin mRNA [5]. Galanin mutant mice have no clear phenotype while maintained on standard chow [88], whereas galanin overexpression increases intake of a HF diet [103]. Galanin protein levels in the PVN are strongly correlated with the consumption of HF diets after 5–6 weeks [5]. In fact, both animals that self-select dietary fat and animals exposed to high levels of dietary fat in a no-choice paradigm have elevated galanin expression in the PVN [119]. It was also shown that in genetically obesity-prone rats, mRNA and protein levels of galanin in the PVN were elevated after HF access, an effect not observed with HS diets or in obesity-resistant rats on a HF diet [61]. These data indicate that galanin may provide positive feedback in response to HF diet consumption, both stimulating and being stimulated by consumption of HF foods.

2.2.2. Blunted effect of anorexigens

Activity of paraventricular neurons synthesizing an anorexigenic peptide oxytocin [154], was found to be down-regulated upon long-term intermittent sugar exposure [138]. We subjected rats to 20 days of scheduled access to a sucrose or cornstarch diet. On the experimental day, activity of oxytocin neurons at the end of a meal was blunted in the rats with extended access to sucrose compared to the cornstarch-treated rats, as shown by *c-fos* levels [138]. Other data support the notion that there is a relationship between the oxytocin system's activity and palatable sugar intake. In oxytocin null mice, intake of non-sweet diets does not differ during ad libitum conditions or during refeeding after an overnight fast [130]. However, oxytocin knock-out mice consumed substantially more of sucrose and saccharin solutions than their wild type littermates [137,184], even after sustained exposure [8]. Also, oxytocin receptor antagonist injections in wild-type mice precipitated an increased preference for sucrose compared to fat [153].

In addition to these effects on the oxytocin system, reduced expression of anorexigenic CART and brain-derived neurotrophic factor (BDNF) was noted during forced abstinence from palatable food [10]. Further, CRH expression in the amygdala and PVN was reduced by extended exposure to a HF diet, and significantly elevated in the amygdala during withdrawal from this diet [205,213].

Whereas the neuropeptidergic adaptations to specific macronutrients described above can shape preference and food choice, it should also be acknowledged that diet-induced obesity entails changes in the signaling of circulating satiety signals such as leptin and insulin. In fact, insulin and leptin resistance develops both peripherally and centrally over time. Insulin infusions into the third ventricle or directly into the ARC decreased food intake and lowered body weight in chow-fed animals, whereas this effect was blunted in rats after access to a HF diet [9,43,69]. In rats maintained on ad libitum chow, intracerebroventricular injections of either insulin or leptin reduced motivation for sucrose as measured by lever pressing on a progressive ratio schedule of reinforcement [70]; however, after 5-week ad libitum access to a HFHS diet, the same doses of leptin and insulin produced no effect [70]. Notably, the animals in this study did not differ in weight, suggesting that although the obese state may accentuate central leptin and insulin insensitivity, diet exposure alone is capable of mediating such effects.

Some mechanisms for leptin resistance have been suggested. Leptin receptor signaling is dependent on the JAK2/STAT3 pathway [23,176] and activation of this pathway stimulates SOC3, a key player in a negative feedback loop that attenuates STAT3 phosphorylation. Deletion of SOC3 from the CNS accordingly increased leptin-mediated phosphorylation of STAT3 and rendered mice

resistant to diet-induced obesity [139]. A more recently suggested mechanism for diet-induced changes in leptin receptor signaling and hypothalamic function is the mammalian target of rapamycin (mTOR). This kinase promotes protein synthesis centrally and peripherally but may also, within the ARC act as a fuel sensor responding to signals such as leptin and plasma nutrients [50]. However, after HF diet treatment in rats, mTOR signaling in the hypothalamus was reduced; these rats did not respond to a leptin treatment, which in low-fat diet-fed controls activated mTOR and decreased food intake [51]. Further, knockout mice lacking mTOR signaling were non-responsive to leptin injections [51]. Thus, HF diets can be speculated to directly affect levels of mTOR activity, which together with SOC3-mediated effects convey central leptin resistance and potentially disinhibit food intake, especially in diet-induced obese animals.

Taken together, it is evident that not only the reward-associated pathways, but also circuits traditionally linked to hunger/satiety display functional adaptations over time in response to palatable diets. From the literature reviewed above, it stands to reason that such plasticity may infer behavioral changes including elevated preference for HF/HS diets or attenuated satiety signaling.

2.3. Diet-induced neural adaptations are not dependent on concomitant obesity

From the literature reviewed here, it becomes evident that sustained neuroadaptations in both “non-homeostatic” reward pathways (dopamine, opioid pathways etc.) and “homeostatic” appetite signaling (NPY, oxytocin etc.) occur in animals during extended exposure to palatable food. Note that these adaptations are sustained even long after the exposure to HF and/or HS diets have been discontinued. Thus, the brain not only seems primed to prefer and overcome palatable, energy-dense food during early exposure to HF and HS tastants, but also displays remarkable plasticity to increase such preference over time, eventually reaching intensified orexigenic states such as food craving, bingeing, and compulsive eating despite negative consequences.

It is crucial to note that these neural and behavioral adaptations do not represent simply the effects of obesity or related factors such as insulin and leptin resistance, elevated plasma glucose levels, or inflammatory processes in tissues. Supporting this renouncement, many of the references above present protocols which do not produce excess weight gain, such as scheduled access to HF/HS diets employed by many groups [7,16,45,55,107,214]. Further, we have shown that some (but not all) addictive-like behaviors and gene expression changes are present in both obesity-prone and obesity-resistant animals [7,167]. Reduced D_2 receptor levels after free access to a cafeteria diet was likewise reported regardless of an obesity phenotype [97]. Nevertheless, it should be acknowledged that, in many cases, it is not possible to separate the effects of excessive consumption of palatable food from the effects of ensuing body fat accrual and metabolic disturbances. Factors more closely related to the obese state, such as elevated plasma triglycerides, or peripheral and central leptin insensitivity, may add to the effects of palatability to create the neurobiological phenotype of diet-induced obese animals after free access to palatable food. However, it seems clear that repeated food reward *per se* has the capacity to induce important neural adaptations, driving addictive-like eating behavior.

The behavioral as well as molecular findings from animal experiments arguably bear relevance also for humans, since addictive-like eating behavior (craving for palatable food) is frequently reported in questionnaire studies. Neural adaptations are also not restricted to animal models, as overeating/weight gain in overweight women was, in a recent longitudinal study, shown to affect the striatal activity in response to palatable food [204]. This seems relevant

throughout the higher end of the body weight spectrum: Wang and colleagues showed [225] that there was an inverse association between BMI and striatal D2 receptor binding in severely obese individuals (BMI range 42–60). Future research should investigate whether these effects are related to overeating *per se* or to the body weight. Also, in the context of altered processing of reward in obese subjects, it is interesting to note that whereas certain genetic variants predispose both drug addiction and obesity [144,201], drug abuse is actually less frequent in obese populations [189]. Based on the preclinical data presented above, it can be tentatively speculated that food reward makes drugs less reinforcing, thus reducing the risk for drug abuse, although further studies are needed to investigate the causal relationship behind this association (drug abuse can arguably be expected to reduce the risk for obesity; see e.g., [226]).

3. Can we stop (over)eating palatable food? Conclusive remarks utilizing the feed-forward model

Palatability is undeniably a profound factor driving our desire to (over)eat and one of the main culprits underlying the current obesity “epidemic”. That tasty, caloric and nutritious foods are most readily consumed is an evolutionarily and physiologically sound phenomenon that serves its purpose in the environment of food scarcity. The function of relatively well defined mechanisms that propel the intake of palatable ingestants occasionally encountered by the individual is therefore intuitively understood. Yet the issue that still puzzles us is why feeding for pleasure during food abundance can so easily get out of control to jeopardize homeostasis and cause short- and long-term negative health consequences. Why is it so difficult to refrain from consuming palatable tastants even though dangers associated with excessive feeding by far outweigh benefits? Based on the wealth of evidence mentioned above, we propose herein a “feed-forward” model illustrating how palatability-motivated food intake progresses to loss-of-control, addictive-like overeating (Fig. 1). We stipulate that neuromolecular changes occurring initially – i.e., upon isolated experiences with palatability – mainly within reward networks, enable the positive (hedonic) reinforcement to be translated into consummatory behavior that may on a given occasion exceed energy needs. Intriguingly, when exposure to palatability is frequent and repetitive, hedonic overeating becomes habitual, which stems from neurobehavioral adaptations that are much more complex and they affect a wider scope of processes controlling reward and motivation as well as those regulating energy balance. Once palatability-driven consumption reaches this habitual level, it enters in fact the vicious cycle of (compulsive) overeating episodes interspaced with cravings precipitated by (in case of dieters) voluntary or (in forced abstinence cases) involuntary hedonic deprivation. It is of particular interest that relapsing into loss-of-control overeating happens not just after a short-term withdrawal from palatability, but also long after new, healthier dietary habits have been established. This indicates that palatability evokes neurobehavioral and molecular adaptations that define our long-term (perhaps, life-long) attitude and responses toward rewarding ingestants. While palatable food restriction methods may be effective in curbing calorie intake (hence, in precipitating weight loss), this is only a transient effect, as they do not really break the vicious cycle of craving and compulsive overeating. They only “mechanically” delay the relapse into excessive consumption, whereas the neuromolecular mechanisms that have already adapted to palatability are always in place to quickly restore previous overeating habits.

Acknowledgments

Preparation of this review was supported by the Swedish Research Council, the Novo Nordisk Foundation and the Swedish

Brain Research Foundation. J.A. was supported in part by the Swedish Academy of Pharmaceutical Sciences.

References

- [1] R.A. Adan, L.J. Vanderschuren, S.E. la Fleur, Anti-obesity drugs and neural circuits of feeding, *Trends Pharmacol. Sci.* 29 (2008) 208–217.
- [2] S.H. Ahmed, G.F. Koob, Transition from moderate to excessive drug intake: change in hedonic set point, *Science* 282 (1998) 298–300.
- [3] S.H. Ahmed, J.R. Walker, G.F. Koob, Persistent increase in the motivation to take heroin in rats with a history of drug escalation, *Neuropsychopharmacology* 22 (2000) 413–421.
- [4] S.H. Ahmed, P.J. Kenny, G.F. Koob, A. Markou, Neurobiological evidence for hedonic allostasis associated with escalating cocaine use, *Nat. Neurosci.* 5 (2002) 625–626.
- [5] A. Akabayashi, J.I. Koenig, Y. Watanabe, J.T. Alexander, S.F. Leibowitz, Galanin-containing neurons in the paraventricular nucleus: a neurochemical marker for fat ingestion and body weight gain, *Proc. Natl. Acad. Sci. USA* 91 (1994) 10375–10379.
- [6] J. Alsiö, C. Pickering, E. Roman, A.L. Hulting, J. Lindblom, H.B. Schiöth, Motivation for sucrose in sated rats is predicted by low anxiety-like behavior, *Neurosci. Lett.* 454 (2009) 193–197.
- [7] J. Alsiö, P.K. Olszewski, A.H. Norback, Z.E. Gunnarsson, A.S. Levine, C. Pickering, H.B. Schiöth, Dopamine D1 receptor gene expression decreases in the nucleus accumbens upon long-term exposure to palatable food and differs depending on diet-induced obesity phenotype in rats, *Neuroscience* 171 (2010) 779–787.
- [8] J.A. Amico, R.R. Vollmer, H.M. Cai, J.A. Miedlar, L. Rinaman, Enhanced initial and sustained intake of sucrose solution in mice with an oxytocin gene deletion, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 289 (2005) R1798–R1806.
- [9] K. Arase, J.S. Fidler, N.S. Shargill, D.A. York, G.A. Bray, Intracerebroventricular infusions of 3-OH-B and insulin in a rat model of dietary obesity, *Am. J. Physiol.* 255 (1988) R974–R981.
- [10] Z.A. Archer, D.V. Rayner, P. Barrett, A. Balik, J.S. Duncan, K.M. Moar, J.G. Mercer, Hypothalamic energy balance gene responses in the Sprague-Dawley rat to supplementation of high-energy diet with liquid ensure and subsequent transfer to chow, *J. Neuroendocrinol.* 17 (2005) 711–719.
- [11] M. Arnone, J. Maruani, F. Chaperon, M.H. Thiebot, M. Poncelet, P. Soubrie, G. Le Fur, Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors, *Psychopharmacology (Berl.)* 132 (1997) 104–106.
- [12] N.M. Avena, B.G. Hoebel, A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine, *Neuroscience* 122 (2003) 17–20.
- [13] N.M. Avena, C.A. Carrillo, L. Needham, S.F. Leibowitz, B.G. Hoebel, Sugar-dependent rats show enhanced intake of unsweetened ethanol, *Alcohol* 34 (2004) 203–209.
- [14] N.M. Avena, K.A. Long, B.G. Hoebel, Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect, *Physiol. Behav.* 84 (2005) 359–362.
- [15] N.M. Avena, P. Rada, N. Moise, B.G. Hoebel, Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response, *Neuroscience* 139 (2006) 813–820.
- [16] N.M. Avena, M.E. Bocarsly, P. Rada, A. Kim, B.G. Hoebel, After daily bingeing on a sucrose solution, food deprivation induces anxiety and accumbens dopamine/acetylcholine imbalance, *Physiol. Behav.* 94 (2008) 309–315.
- [17] N.M. Avena, P. Rada, B.G. Hoebel, Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake, *Neurosci. Biobehav. Rev.* 32 (2008) 20–39.
- [18] N.M. Avena, P. Rada, B.G. Hoebel, Sugar and fat bingeing have notable differences in addictive-like behavior, *J. Nutr.* 139 (2009) 623–628.
- [19] M.J. Barnes, K. Lapanowski, A. Conley, J.A. Rafols, K.L. Jen, J.C. Dunbar, High fat feeding is associated with increased blood pressure, sympathetic nerve activity and hypothalamic mu opioid receptors, *Brain Res. Bull.* 61 (2003) 511–519.
- [20] M. Barrot, J.D. Olivier, L.I. Perrotti, R.J. DiLeone, O. Berton, A.J. Eisch, S. Impey, D.R. Storm, R.L. Neve, J.C. Yin, V. Zachariou, E.J. Nestler, CREB activity in the nucleus accumbens shell controls gating of behavioral responses to emotional stimuli, *Proc. Natl. Acad. Sci. USA* 99 (2002) 11435–11440.
- [21] V. Bassareo, G. Di Chiara, Differential influence of associative and nonassociative learning mechanisms on the responsiveness of prefrontal and accumbal dopamine transmission to food stimuli in rats fed ad libitum, *J. Neurosci.* 17 (1997) 851–861.
- [22] V. Bassareo, G. Di Chiara, Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state, *Eur. J. Neurosci.* 11 (1999) 4389–4397.
- [23] S.H. Bates, W.H. Stearns, T.A. Dundon, M. Schubert, A.W. Tso, Y. Wang, A.S. Banks, H.J. Lavery, A.K. Haq, E. Maratos-Flier, B.G. Neel, M.W. Schwartz, M.G. Myers Jr., STAT3 signalling is required for leptin regulation of energy balance but not reproduction, *Nature* 421 (2003) 856–859.
- [24] T.R. Beckman, Q. Shi, A.S. Levine, C.J. Billington, Amygdalar opioids modulate hypothalamic melanocortin-induced anorexia, *Physiol. Behav.* 96 (2009) 568–573.

- [25] L. Bellocchio, P. Lafenetre, A. Cannich, D. Cota, N. Puente, P. Grandes, F. Chaouloff, P.V. Piazza, G. Marsicano, Bimodal control of stimulated food intake by the endocannabinoid system, *Nat. Neurosci.* 13 (2010) 281–283.
- [26] E. Benito, A. Barco, CREB's control of intrinsic and synaptic plasticity: implications for CREB-dependent memory models, *Trends Neurosci.* 33 (2010) 230–240.
- [27] L.A. Berner, N.M. Avena, B.G. Hoebel, Bingeing, self-restriction, and increased body weight in rats with limited access to a sweet-fat diet, *Obesity (Silver Spring)* 16 (2008) 1998–2002.
- [28] K.C. Berridge, T.E. Robinson, What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience?, *Brain Res Brain Res. Rev.* 28 (1998) 309–369.
- [29] H.R. Berthoud, Homeostatic and non-homeostatic pathways involved in the control of food intake and energy balance, *Obesity (Silver Spring)* 14 (Suppl. 5) (2006) 1975–2005.
- [30] H.R. Berthoud, N.R. Lenard, A.C. Shin, Food reward, hyperphagia, and obesity, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 300 (2011) R1266–R1277.
- [31] O. Berton, H.E. Covington III, K. Ebner, N.M. Tsankova, T.L. Carle, P. Ulerly, A. Bhoonle, M. Barrot, V. Krishnan, G.M. Singewald, N. Singewald, S. Birnbaum, R.L. Neve, E.J. Nestler, Induction of deltaFosB in the periaqueductal gray by stress promotes active coping responses, *Neuron* 55 (2007) 289–300.
- [32] M. Bluher, S. Engeli, N. Klotting, J. Berndt, M. Fasshauer, S. Batkai, P. Pacher, M.R. Schon, J. Jordan, M. Stunvoll, Dysregulation of the peripheral and adipose tissue endocannabinoid system in human abdominal obesity, *Diabetes* 55 (2006) 3053–3060.
- [33] R. Bourchouladze, B. Frenguelli, J. Blendy, D. Cioffi, G. Schutz, A.J. Silva, Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein, *Cell* 79 (1994) 59–68.
- [34] C. Braet, L. Claus, L. Goossens, E. Moens, L. Van Vlierbergh, B. Soetens, Differences in eating style between overweight and normal-weight youngsters, *J. Health Psychol.* 13 (2008) 733–743.
- [35] L.A. Briand, S.B. Fligel, P. Seeman, T.E. Robinson, Cocaine self-administration produces a persistent increase in dopamine D2 High receptors, *Eur. Neuropsychopharmacol.* 18 (2008) 551–556.
- [36] P. Burton, H.J. Smit, H.J. Lightowler, The influence of restrained and external eating patterns on overeating, *Appetite* 49 (2007) 191–197.
- [37] M. Cador, A.E. Kelley, M. Le Moal, L. Stinus, Ventral tegmental area infusion of substance P, neurotensin and enkephalin: differential effects on feeding behavior, *Neuroscience* 18 (1986) 659–669.
- [38] L. Cantin, M. Lenoir, E. Augier, N. Vanhille, S. Dubreucq, F. Serre, C. Vouillac, S.H. Ahmed, Cocaine is low on the value ladder of rats: possible evidence for resilience to addiction, *PLoS ONE* 5 (2010) e11592.
- [39] W.A. Carlezon Jr., J. Thome, V.G. Olson, S.B. Lane-Ladd, E.S. Brodtkin, N. Hiroi, R.S. Duman, R.L. Neve, E.J. Nestler, Regulation of cocaine reward by CREB, *Science* 282 (1998) 2272–2275.
- [40] W.A. Carlezon Jr., R.S. Duman, E.J. Nestler, The many faces of CREB, *Trends Neurosci.* 28 (2005) 436–445.
- [41] M.E. Carroll, S.T. Lac, Dietary additives and the acquisition of cocaine self-administration in rats, *Psychopharmacology (Berl.)* 137 (1998) 81–89.
- [42] M.E. Carroll, C.P. France, R.A. Meisch, Intravenous self-administration of etonitazene, cocaine and phencyclidine in rats during food deprivation and satiation, *J. Pharmacol. Exp. Ther.* 217 (1981) 241–247.
- [43] M. Chavez, C.A. Riedy, G. Van Dijk, S.C. Woods, Central insulin and macronutrient intake in the rat, *Am. J. Physiol.* 271 (1996) R727–R731.
- [44] R. Christensen, P.K. Kristensen, E.M. Bartels, H. Bliddal, A. Astrup, Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials, *Lancet* 370 (2007) 1706–1713.
- [45] A.M. Christiansen, A.D. Dekloet, Y.M. Ulrich-Lai, J.P. Herman, “Snacking” causes long term attenuation of HPA axis stress responses and enhancement of brain FosB/deltaFosB expression in rats, *Physiol. Behav.* 103 (2011) 111–116.
- [46] J.S. Coelho, J. Polivy, C.P. Herman, Selective carbohydrate or protein restriction: effects on subsequent food intake and cravings, *Appetite* 47 (2006) 352–360.
- [47] C. Colantuoni, J. Schwenker, J. McCarthy, P. Rada, B. Ladenheim, J.L. Cadet, G.J. Schwartz, T.H. Moran, B.G. Hoebel, Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain, *NeuroReport* 12 (2001) 3549–3552.
- [48] C. Colantuoni, P. Rada, J. McCarthy, C. Patten, N.M. Avena, A. Chadeayne, B.G. Hoebel, Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence, *Obes. Res.* 10 (2002) 478–488.
- [49] C.R. Colby, K. Whisler, C. Steffen, E.J. Nestler, D.W. Self, Striatal cell type-specific overexpression of DeltaFosB enhances incentive for cocaine, *J. Neurosci.* 23 (2003) 2488–2493.
- [50] D. Cota, K. Proulx, K.A. Smith, S.C. Kozma, G. Thomas, S.C. Woods, R.J. Seeley, Hypothalamic mTOR signaling regulates food intake, *Science* 312 (2006) 927–930.
- [51] D. Cota, E.K. Matter, S.C. Woods, R.J. Seeley, The role of hypothalamic mammalian target of rapamycin complex 1 signaling in diet-induced obesity, *J. Neurosci.* 28 (2008) 7202–7208.
- [52] P. Cottone, V. Sabino, L. Steardo, E.P. Zorrilla, Intermittent access to preferred food reduces the reinforcing efficacy of chow in rats, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 295 (2008) R1066–R1076.
- [53] M.F. Dallman, N.C. Pecoraro, S.E. la Fleur, Chronic stress and comfort foods: self-medication and abdominal obesity, *Brain Behav. Immun.* 19 (2005) 275–280.
- [54] K.W. Davis, P.J. Wellman, P.S. Clifford, Augmented cocaine conditioned place preference in rats pretreated with systemic ghrelin, *Regul. Pept.* 140 (2007) 148–152.
- [55] J.F. Davis, A.L. Tracy, J.D. Schurdak, M.H. Tschoep, J.W. Lipton, D.J. Clegg, S.C. Benoit, Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat, *Behav. Neurosci.* 122 (2008) 1257–1263.
- [56] N.J. DeSousa, D.E. Bush, F.J. Vaccarino, Self-administration of intravenous amphetamine is predicted by individual differences in sucrose feeding in rats, *Psychopharmacology (Berl.)* 148 (2000) 52–58.
- [57] G. Di Chiara, A. Imperato, Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats, *Proc. Natl. Acad. Sci. USA* 85 (1988) 5274–5278.
- [58] G. Di Chiara, A. Imperato, Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats, *J. Pharmacol. Exp. Ther.* 244 (1988) 1067–1080.
- [59] V. Di Marzo, S.K. Goparaju, L. Wang, J. Liu, S. Batkai, Z. Jarai, F. Fezza, G.I. Miura, R.D. Palmiter, T. Sugiura, G. Kunos, Leptin-regulated endocannabinoids are involved in maintaining food intake, *Nature* 410 (2001) 822–825.
- [60] V. Di Marzo, A. Ligresti, L. Cristino, The endocannabinoid system as a link between homeostatic and hedonic pathways involved in energy balance regulation, *Int. J. Obes. (Lond.)* 33 (Suppl. 2) (2009) S18–S24.
- [61] J.T. Dourmashkin, G.Q. Chang, E.C. Gayles, J.O. Hill, S.K. Fried, C. Julien, S.F. Leibowitz, Different forms of obesity as a function of diet composition, *Int. J. Obes. (Lond.)* 29 (2005) 1368–1378.
- [62] W.C. Drevets, C. Gautier, J.C. Price, D.J. Kupfer, P.E. Kinahan, A.A. Grace, J.L. Price, C.A. Mathis, Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria, *Biol. Psychiatry* 49 (2001) 81–96.
- [63] E. Eggecioglu, E. Jerlhag, N. Salome, K.P. Skibicka, D. Haage, Y.M. Bohlooly, D. Andersson, M. Bjursell, D. Perrissoud, J.A. Engel, S.L. Dickson, Ghrelin increases intake of rewarding food in rodents, *Addict. Biol.* 15 (2010) 304–311.
- [64] K.R. Evans, F.J. Vaccarino, Amphetamine- and morphine-induced feeding: evidence for involvement of reward mechanisms, *Neurosci. Biobehav. Rev.* 14 (1990) 9–22.
- [65] B.J. Everitt, T.W. Robbins, Neural systems of reinforcement for drug addiction: from actions to habits to compulsion, *Nat. Neurosci.* 8 (2005) 1481–1489.
- [66] B.J. Everitt, A. Dickinson, T.W. Robbins, The neuropsychological basis of addictive behaviour, *Brain Res. Brain Res. Rev.* 36 (2001) 129–138.
- [67] M. Fantino, J. Hosotte, M. Apfelbaum, An opioid antagonist, naltrexone, reduces preference for sucrose in humans, *Am. J. Physiol.* 251 (1986) R91–R96.
- [68] I.S. Farooqi, E. Bullmore, J. Keogh, J. Gillard, S. O'Rahilly, P.C. Fletcher, Leptin regulates striatal regions and human eating behavior, *Science* 317 (2007) 1355.
- [69] D.P. Figlewicz, A. Zavosh, T. Sexton, J.F. Neumaier, Catabolic action of insulin in rat arcuate nucleus is not enhanced by exogenous “tub” expression, *Am. J. Physiol. Endocrinol. Metab.* 286 (2004) E1004–E1010.
- [70] D.P. Figlewicz, J.L. Bennett, A.M. Naleid, C. Davis, J.W. Grimm, Intraventricular insulin and leptin decrease sucrose self-administration in rats, *Physiol. Behav.* 89 (2006) 611–616.
- [71] B.M. Geiger, M. Haburcak, N.M. Avena, M.C. Moyer, B.G. Hoebel, E.N. Pothos, Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity, *Neuroscience* 159 (2009) 1193–1199.
- [72] C.H. Gilhooly, S.K. Das, J.K. Golden, M.A. McCrory, G.E. Dallal, E. Saltzman, F.M. Kramer, S.B. Roberts, Food cravings and energy regulation: the characteristics of craved foods and their relationship with eating behaviors and weight change during 6 months of dietary energy restriction, *Int. J. Obes. (Lond.)* 31 (2007) 1849–1858.
- [73] S.Q. Giraud, M.K. Grace, C.C. Welch, C.J. Billington, A.S. Levine, Naloxone's anorectic effect is dependent upon the relative palatability of food, *Pharmacol. Biochem. Behav.* 46 (1993) 917–921.
- [74] M.J. Glass, C.J. Billington, A.S. Levine, Naltrexone administered to central nucleus of amygdala or PVN: neural dissociation of diet and energy, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 279 (2000) R86–R92.
- [75] M.J. Glass, M. Grace, J.P. Cleary, C.J. Billington, A.S. Levine, Potency of naloxone's anorectic effect in rats is dependent on diet preference, *Am. J. Physiol.* 271 (1996) R217–R221.
- [76] R.Z. Goldstein, N. Alia-Klein, D. Tomasi, L. Zhang, L.A. Cottone, T. Maloney, F. Telang, E.C. Caparelli, L. Chang, T. Ernst, D. Samaras, N.K. Squires, N.D. Volkow, Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction?, *Am. J. Psychiatry* 164 (2007) 43–51.
- [77] B.A. Gosnell, Sucrose intake predicts rate of acquisition of cocaine self-administration, *Psychopharmacology (Berl.)* 149 (2000) 286–292.
- [78] B.A. Gosnell, Sucrose intake enhances behavioral sensitization produced by cocaine, *Brain Res.* 1031 (2005) 194–201.
- [79] B.A. Gosnell, D.D. Krahn, M.J. Majchrzak, The effects of morphine on diet selection are dependent upon baseline diet preferences, *Pharmacol. Biochem. Behav.* 37 (1990) 207–212.
- [80] C.G. Greeno, R.R. Wing, S. Shiffman, Binge antecedents in obese women with and without binge eating disorder, *J. Consult. Clin. Psychol.* 68 (2000) 95–102.
- [81] M.M. Hagan, P.A. Rushing, S.C. Benoit, S.C. Woods, R.J. Seeley, Opioid receptor involvement in the effect of AgRP- (83–132) on food intake and food selection, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 280 (2001) R814–R821.

- [82] A. Hajnal, W.M. Margas, M. Covasa, Altered dopamine D2 receptor function and binding in obese OLETF rat, *Brain Res. Bull.* 75 (2008) 70–76.
- [83] A. Hamdi, J. Porter, C. Prasad, Decreased striatal D2 dopamine receptors in obese Zucker rats: changes during aging, *Brain Res.* 589 (1992) 338–340.
- [84] J.A. Harrold, J.C. Elliott, P.J. King, P.S. Widdowson, G. Williams, Down-regulation of cannabinoid-1 (CB-1) receptors in specific extrahypothalamic regions of rats with dietary obesity: a role for endogenous cannabinoids in driving appetite for palatable food?, *Brain Res* 952 (2002) 232–238.
- [85] A. Heyne, C. Kiesselbach, I. Sahun, J. McDonald, M. Gaiffi, M. Dierssen, J. Wolffgramm, An animal model of compulsive food-taking behaviour, *Addict. Biol.* 14 (2009) 373–383.
- [86] A.J. Hill, The psychology of food craving, *Proc. Nutr. Soc.* 66 (2007) 277–285.
- [87] A.J. Hill, C.F. Weaver, J.E. Blundell, Food craving, dietary restraint and mood, *Appetite* 17 (1991) 187–197.
- [88] J.G. Hohmann, S.M. Krasnow, D.N. Teklemichael, D.K. Clifton, D. Wynick, R.A. Steiner, Neuroendocrine profiles in galanin-overexpressing and knockout mice, *Neuroendocrinology* 77 (2003) 354–366.
- [89] J.D. Hommel, R. Trinko, R.M. Sears, D. Georgescu, Z.W. Liu, X.B. Gao, J.J. Thurmon, M. Marinelli, R.J. DiLeone, Leptin receptor signaling in midbrain dopamine neurons regulates feeding, *Neuron* 51 (2006) 801–810.
- [90] J. Horder, C.J. Harmer, P.J. Cowen, C. McCabe, Reduced neural response to reward following 7 days treatment with the cannabinoid CB1) antagonist rimonabant in healthy volunteers, *Int. J. Neuropsychopharmacol.* 13 (2010) 1103–1113.
- [91] T.L. Horvath, X.B. Gao, Input organization and plasticity of hypocretin neurons: possible clues to obesity's association with insomnia, *Cell Metab.* 1 (2005) 279–286.
- [92] X.F. Huang, Y. Yu, K. Zavitsanos, M. Han, L. Storlien, Differential expression of dopamine D2 and D4 receptor and tyrosine hydroxylase mRNA in mice prone, or resistant, to chronic high-fat diet-induced obesity, *Brain Res. Mol. Brain Res.* 135 (2005) 150–161.
- [93] J.H. Jaffe, N.G. Cascella, K.M. Kumor, M.A. Sherer, Cocaine-induced cocaine craving, *Psychopharmacology (Berl.)* 97 (1989) 59–64.
- [94] O. Jbilo, C. Ravinet-Trillou, M. Arnone, I. Buisson, E. Bribeas, A. Peleraux, G. Penarier, P. Soubrie, G. Le Fur, S. Galiegue, P. Casellas, The CB1 receptor antagonist rimonabant reverses the diet-induced obesity phenotype through the regulation of lipolysis and energy balance, *FASEB J.* 19 (2005) 1567–1569.
- [95] E. Jerlhag, E. Eggecioglu, S. Landgren, N. Salome, M. Heilig, D. Moechars, R. Datta, D. Perrissoud, S.L. Dickson, J.A. Engel, Requirement of central ghrelin signaling for alcohol reward, *Proc. Natl. Acad. Sci. USA* 106 (2009) 11318–11323.
- [96] A. Johansson, R. Fredriksson, S. Winnergren, A.L. Hulting, H.B. Schioth, J. Lindblom, The relative impact of chronic food restriction and acute food deprivation on plasma hormone levels and hypothalamic neuropeptide expression, *Peptides* 29 (2008) 1588–1595.
- [97] P.M. Johnson, P.J. Kenny, Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats, *Nat. Neurosci.* 13 (2010) 635–641.
- [98] S.W. Johnson, R.A. North, Opioids excite dopamine neurons by hyperpolarization of local interneurons, *J. Neurosci.* 12 (1992) 483–488.
- [99] S.A. Josselyn, C. Shi, W.A. Carlezon Jr., R.L. Neve, E.J. Nestler, M. Davis, Long-term memory is facilitated by cAMP response element-binding protein overexpression in the amygdala, *J. Neurosci.* 21 (2001) 2404–2412.
- [100] P.W. Kalivas, C. O'Brien, Drug addiction as a pathology of staged neuroplasticity, *Neuropsychopharmacology* 33 (2008) 166–180.
- [101] R.B. Kanarek, W.F. Mathes, J. Przybeck, Intake of dietary sucrose or fat reduces amphetamine drinking in rats, *Pharmacol. Biochem. Behav.* 54 (1996) 719–723.
- [102] S.E. Kanoski, M.R. Hayes, H.S. Greenwald, S.M. Fortin, C.A. Gianessi, J.R. Gilbert, H.J. Grill, Hippocampal leptin signaling reduces food intake and modulates food-related memory processing, *Neuropsychopharmacology* 36 (2011) 1859–1870.
- [103] O. Karatayev, J. Baylan, S.F. Leibowitz, Increased intake of ethanol and dietary fat in galanin overexpressing mice, *Alcohol* 43 (2009) 571–580.
- [104] L.J. Karhunen, R.I. Lappalainen, E.J. Vanninen, J.T. Kuikka, M.I. Uusitupa, Regional cerebral blood flow during food exposure in obese and normal-weight women, *Brain* 120 (Pt. 9) (1997) 1675–1684.
- [105] F. Kasanetz, V. Deroche-Gamonet, N. Berson, E. Balado, M. Lafourcade, O. Manzoni, P.V. Piazza, Transition to addiction is associated with a persistent impairment in synaptic plasticity, *Science* 328 (2010) 1709–1712.
- [106] Y. Katsuura, J.A. Heckmann, S.A. Taha, mu-Opioid receptor stimulation in the nucleus accumbens elevates fatty tastant intake by increasing palatability and suppressing satiety signals, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 301 (2011) R244–R254.
- [107] A.E. Kelley, M.J. Will, T.L. Steininger, M. Zhang, S.N. Haber, Restricted daily consumption of a highly palatable food (chocolate Ensure(R)) alters striatal enkephalin gene expression, *Eur. J. Neurosci.* 18 (2003) 2592–2598.
- [108] A.E. Kelley, B.A. Baldo, W.E. Pratt, M.J. Will, Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward, *Physiol. Behav.* 86 (2005) 773–795.
- [109] P.J. Kenny, Tobacco dependence, the insular cortex and the hypocretin connection, *Pharmacol. Biochem. Behav.* 97 (2011) 700–707.
- [110] P.J. Kenny, S.A. Chen, O. Kitamura, A. Markou, G.F. Koob, Conditioned withdrawal drives heroin consumption and decreases reward sensitivity, *J. Neurosci.* 26 (2006) 5894–5900.
- [111] S. Komatsu, Rice and sushi cravings: a preliminary study of food craving among Japanese females, *Appetite* 50 (2008) 353–358.
- [112] G.F. Koob, F.E. Bloom, Cellular and molecular mechanisms of drug dependence, *Science* 242 (1988) 715–723.
- [113] G.F. Koob, E.P. Zorrilla, Neurobiological mechanisms of addiction: focus on corticotropin-releasing factor, *Curr. Opin. Invest. Drugs* 11 (2010) 63–71.
- [114] S.E. Kyrkouli, B.G. Stanley, R.D. Seirafi, S.F. Leibowitz, Stimulation of feeding by galanin: anatomical localization and behavioral specificity of this peptide's effects in the brain, *Peptides* 11 (1990) 995–1001.
- [115] S.E. la Fleur, L.J. Vanderschuren, M.C. Luijendijk, B.M. Kloeze, B. Tiesjema, R.A. Adan, A reciprocal interaction between food-motivated behavior and diet-induced obesity, *Int. J. Obes. (Lond.)* 31 (2007) 1286–1294.
- [116] S.E. la Fleur, A.J. van Rozen, M.C. Luijendijk, F. Groeneweg, R.A. Adan, A free-choice high-fat high-sugar diet induces changes in arcuate neuropeptide expression that support hyperphagia, *Int. J. Obes. (Lond.)* (2009).
- [117] J. Le Merrer, D.N. Stephens, Food-induced behavioral sensitization, its cross-sensitization to cocaine and morphine, pharmacological blockade, and effect on food intake, *J. Neurosci.* 26 (2006) 7163–7171.
- [118] L. Leggio, Understanding and treating alcohol craving and dependence: Recent pharmacological and neuroendocrinological findings, *Alcohol Alcohol.* 44 (2009) 341–352.
- [119] S.F. Leibowitz, A. Akabayashi, J. Wang, Obesity on a high-fat diet: role of hypothalamic galanin in neurons of the anterior paraventricular nucleus projecting to the median eminence, *J. Neurosci.* 18 (1998) 2709–2719.
- [120] N.R. Lenard, H. Zheng, H.R. Berthoud, Chronic suppression of mu-opioid receptor signaling in the nucleus accumbens attenuates development of diet-induced obesity in rats, *Int. J. Obes. (Lond.)* 34 (2010) 1001–1010.
- [121] B.E. Levin, A.A. Dunn-Meynell, Defense of body weight depends on dietary composition and palatability in rats with diet-induced obesity, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 282 (2002) R46–R54.
- [122] B.E. Levin, A.A. Dunn-Meynell, B. Balkan, R.E. Keesey, Selective breeding for diet-induced obesity and resistance in Sprague-Dawley rats, *Am. J. Physiol.* 273 (1997) R725–R730.
- [123] A.S. Levine, S.S. Murray, J. Kneip, M. Grace, J.E. Morley, Flavor enhances the antidipsogenic effect of naloxone, *Physiol. Behav.* 28 (1982) 23–25.
- [124] A.S. Levine, D.T. Weldon, M. Grace, J.P. Cleary, C.J. Billington, Naloxone blocks that portion of feeding driven by sweet taste in food-restricted rats, *Am. J. Physiol.* 268 (1995) R248–R252.
- [125] M. Lutter, E.J. Nestler, Homeostatic and hedonic signals interact in the regulation of food intake, *J. Nutr.* 139 (2009) 629–632.
- [126] W.C. Lynch, Opiate blockade inhibits saccharin intake and blocks normal preference acquisition, *Pharmacol. Biochem. Behav.* 24 (1986) 833–836.
- [127] W.C. Lynch, M. Grace, C.J. Billington, A.S. Levine, Effects of neuropeptide Y on ingestion of flavored solutions in nondeprived rats, *Physiol. Behav.* 54 (1993) 877–880.
- [128] N.H. Majeed, B. Przewlocka, K. Wedzony, R. Przewlocki, Stimulation of food intake following opioid microinjection into the nucleus accumbens septi in rats, *Peptides* 7 (1986) 711–716.
- [129] S. Malik, F. McGlone, D. Bedrossian, A. Dagher, Ghrelin modulates brain activity in areas that control appetitive behavior, *Cell Metab.* 7 (2008) 400–409.
- [130] R.C. Mantella, L. Rinaman, R.R. Vollmer, J.A. Amico, Cholecystokinin and D-fenfluramine inhibit food intake in oxytocin-deficient mice, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 285 (2003) R1037–R1045.
- [131] E. Martin-Garcia, A. Burokas, E. Kostrozewa, A. Gierzyk, M. Korostynski, B. Ziolkowska, B. Przewlocka, R. Przewlocki, R. Maldonado, New operant model of reinstatement of food-seeking behavior in mice, *Psychopharmacology (Berl.)* 215 (2011) 49–70.
- [132] F. Massa, G. Mancini, H. Schmidt, F. Steindel, K. Mackie, C. Angioni, S.H. Oliet, G. Geisslinger, B. Lutz, Alterations in the hippocampal endocannabinoid system in diet-induced obese mice, *J. Neurosci.* 30 (2010) 6273–6281.
- [133] I. Maze, H.E. Covington 3rd, D.M. Dietz, Q. LaPlant, W. Renthal, S.J. Russo, M. Mechanic, E. Mouzoun, Y.L. Neve, S.J. Haggarty, Y. Ren, S.C. Sampath, Y.L. Hurd, P. Greengard, A. Tarakhovskiy, A. Schaefer, E.J. Nestler, Essential role of the histone methyltransferase G9a in cocaine-induced plasticity, *Science* 327 (2010) 213–216.
- [134] C.A. McClung, E.J. Nestler, Regulation of gene expression and cocaine reward by CREB and DeltaFosB, *Nat. Neurosci.* 6 (2003) 1208–1215.
- [135] C.A. McClung, P.G. Ulerly, L.I. Perrotti, V. Zachariou, O. Berton, E.J. Nestler, DeltaFosB: a molecular switch for long-term adaptation in the brain, *Brain Res. Mol. Brain Res.* 132 (2004) 146–154.
- [136] J.G. Mercer, Z.A. Archer, Diet-induced obesity in the Sprague-Dawley rat: dietary manipulations and their effect on hypothalamic neuropeptide energy balance systems, *Biochem. Soc. Trans.* 33 (2005) 1068–1072.
- [137] J.A. Miedlar, L. Rinaman, R.R. Vollmer, J.A. Amico, Oxytocin gene deletion mice overconsume palatable sucrose solution but not palatable lipid emulsions, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 293 (2007) R1063–R1068.
- [138] A. Mitra, B.A. Gosnell, H.B. Schioth, M.K. Grace, A. Klockars, P.K. Olszewski, A.S. Levine, Chronic sugar intake dampens feeding-related activity of neurons synthesizing a satiety mediator, oxytocin, *Peptides* 31 (2010) 1346–1352.
- [139] H. Mori, R. Hanada, T. Hanada, D. Aki, R. Mashima, H. Nishinakamura, T. Torisu, K.R. Chien, H. Yasukawa, A. Yoshimura, Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity, *Nat. Med.* 10 (2004) 739–743.
- [140] J.E. Morley, A.S. Levine, B.A. Gosnell, J. Kneip, M. Grace, Effect of neuropeptide Y on ingestive behaviors in the rat, *Am. J. Physiol.* 252 (1987) R599–R609.

- [141] M. Nakazato, N. Murakami, Y. Date, M. Kojima, H. Matsuo, K. Kangawa, S. Matsukura, A role for ghrelin in the central regulation of feeding, *Nature* 409 (2001) 194–198.
- [142] A.M. Naleid, M.K. Grace, M. Chimukangara, C.J. Billington, A.S. Levine, Paraventricular opioids alter intake of high-fat but not high-sucrose diet depending on diet preference in a binge model of feeding, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 293 (2007) R99–R105.
- [143] E.J. Nestler, M. Barrot, D.W. Self, DeltaFosB: a sustained molecular switch for addiction, *Proc. Natl. Acad. Sci. USA* 98 (2001) 11042–11046.
- [144] E.P. Noble, Addiction and its reward process through polymorphisms of the D2 dopamine receptor gene: a review, *Eur. Psychiatry* 15 (2000) 79–89.
- [145] M.B. Noel, R.A. Wise, Ventral tegmental injections of morphine but not U-50,488H enhance feeding in food-deprived rats, *Brain Res.* 632 (1993) 68–73.
- [146] M.B. Noel, R.A. Wise, Ventral tegmental injections of a selective mu or delta opioid enhance feeding in food-deprived rats, *Brain Res.* 673 (1995) 304–312.
- [147] J.P. O'Doherty, R. Deichmann, H.D. Critchley, R.J. Dolan, Neural responses during anticipation of a primary taste reward, *Neuron* 33 (2002) 815–826.
- [148] M. Odorizzi, J.P. Max, P. Tankosic, C. Burlet, A. Burlet, Dietary preferences of Brattleboro rats correlated with an overexpression of galanin in the hypothalamus, *Eur. J. Neurosci.* 11 (1999) 3005–3014.
- [149] P. Olsson, J.D. Jentsch, N. Tronson, R.L. Neve, E.J. Nestler, J.R. Taylor, DeltaFosB in the nucleus accumbens regulates food-reinforced instrumental behavior and motivation, *J. Neurosci.* 26 (2006) 9196–9204.
- [150] C.M. Olsen, Natural rewards, neuroplasticity, and non-drug addictions, *Neuropharmacology* 61 (2011) 1109–1122.
- [151] P.K. Olszewski, J. Cedernaes, F. Olsson, A.S. Levine, H.B. Schiöth, Analysis of the network of feeding neuroregulators using the Allen Brain Atlas, *Neurosci. Biobehav. Rev.* 32 (2008) 945–956.
- [152] P.K. Olszewski, T.J. Shaw, M.K. Grace, C.E. Hoglund, R. Fredriksson, H.B. Schiöth, A.S. Levine, Complexity of neural mechanisms underlying overconsumption of sugar in scheduled feeding: involvement of opioids, orexin, oxytocin and NPY, *Peptides* 30 (2009) 226–233.
- [153] P.K. Olszewski, A. Klockars, A.M. Olszewska, R. Fredriksson, H.B. Schiöth, A.S. Levine, Molecular, immunohistochemical, and pharmacological evidence of oxytocin's role as inhibitor of carbohydrate but not fat intake, *Endocrinology* 151 (2010) 4736–4744.
- [154] P.K. Olszewski, A. Klockars, H.B. Schiöth, A.S. Levine, Oxytocin as feeding inhibitor: maintaining homeostasis in consummatory behavior, *Pharmacol. Biochem. Behav.* 97 (2010) 47–54.
- [155] P.K. Olszewski, J. Alsiö, H.B. Schiöth, A.S. Levine, Opioids as facilitators of feeding: can any food be rewarding?, *Physiol. Behav.* 104 (2011) 105–110.
- [156] L. Orio, S. Edwards, O. George, L.H. Parsons, G.F. Koob, A role for the endocannabinoid system in the increased motivation for cocaine in extended-access conditions, *J. Neurosci.* 29 (2009) 4846–4857.
- [157] M. Orozco, C. Rouch, V. Dauge, Behavioral responses to ingestion of different sources of fat. Involvement of serotonin?, *Behav. Brain Res.* 132 (2002) 103–109.
- [158] L.A. Parker, S. Maier, M. Rennie, J. Crebolder, Morphine- and naltrexone-induced modification of palatability: analysis by the taste reactivity test, *Behav. Neurosci.* 106 (1992) 999–1010.
- [159] S. Pecina, K.C. Berridge, Opioid site in nucleus accumbens shell mediates eating and hedonic 'liking' for food: map based on microinjection Fos plumes, *Brain Res.* 863 (2000) 71–86.
- [160] S. Pecina, K.C. Berridge, Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness?, *J. Neurosci.* 25 (2005) 11777–11786.
- [161] S. Pecina, B. Cagniard, K.C. Berridge, J.W. Aldridge, X. Zhuang, Hyperdopaminergic mutant mice have higher "wanting" but not "liking" for sweet rewards, *J. Neurosci.* 23 (2003) 9395–9402.
- [162] M.L. Pelchat, Food cravings in young and elderly adults, *Appetite* 28 (1997) 103–113.
- [163] M.L. Pelchat, S. Schaefer, Dietary monotony and food cravings in young and elderly adults, *Physiol. Behav.* 68 (2000) 353–359.
- [164] M.L. Pelchat, A. Johnson, R. Chan, J. Valdez, J.D. Ragland, Images of desire: food-craving activation during fMRI, *Neuroimage* 23 (2004) 1486–1493.
- [165] L.I. Perrotti, R.R. Weaver, B. Robinson, W. Renthal, I. Maze, S. Yazdani, R.G. Elmore, D.J. Knapp, D.E. Selley, B.R. Martin, L. Sim-Selley, R.K. Bachtell, D.W. Self, E.J. Nestler, Distinct patterns of DeltaFosB induction in brain by drugs of abuse, *Synapse* 62 (2008) 358–369.
- [166] G.D. Petrovich, C.A. Ross, M. Gallagher, P.C. Holland, Learned contextual cue potentiates eating in rats, *Physiol. Behav.* 90 (2007) 362–367.
- [167] C. Pickering, J. Alsiö, A.L. Hulting, H.B. Schiöth, Withdrawal from free-choice high-fat high-sugar diet induces craving only in obesity-prone animals, *Psychopharmacology (Berl.)* 204 (2009) 431–443.
- [168] R.C. Pierce, L.J. Vanderschuren, Kicking the habit: the neural basis of ingrained behaviors in cocaine addiction, *Neurosci. Biobehav. Rev.* 35 (2010) 212–219.
- [169] S. Pinto, A.G. Roseberry, H. Liu, S. Diano, M. Shanabrough, X. Cai, J.M. Friedman, T.L. Horvath, Rapid rewiring of arcuate nucleus feeding circuits by leptin, *Science* 304 (2004) 110–115.
- [170] J. Polivy, J. Coleman, C.P. Herman, The effect of deprivation on food cravings and eating behavior in restrained and unrestrained eaters, *Int. J. Eat. Disord.* 38 (2005) 301–309.
- [171] J.D. Pomonis, D.C. Jewett, C.M. Kotz, J.E. Briggs, C.J. Billington, A.S. Levine, Sucrose consumption increases naloxone-induced c-Fos immunoreactivity in limbic forebrain, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 278 (2000) R712–R719.
- [172] A. Prasad, C. Prasad, Short-term consumption of a diet rich in fat decreases anxiety response in adult male rats, *Physiol. Behav.* 60 (1996) 1039–1042.
- [173] C. Quarta, L. Bellocchio, G. Mancini, R. Mazza, C. Cervino, L.J. Braulke, C. Fekete, R. Latorre, C. Nanni, M. Bucci, L.E. Clemens, G. Heldmaier, M. Watanabe, T. Leste-Lassere, M. Maitre, L. Tedesco, F. Fanelli, S. Reuss, S. Klaus, R.K. Srivastava, K. Monory, A. Valerio, A. Grandis, R. De Giorgio, R. Pasquali, E. Nisoli, D. Cota, B. Lutz, G. Marsicano, U. Pagotto, CB(1) signaling in forebrain and sympathetic neurons is a key determinant of endocannabinoid actions on energy balance, *Cell Metab.* 11 (2010) 273–285.
- [174] P. Rada, N.M. Avena, B.G. Hoebel, Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell, *Neuroscience* 134 (2005) 737–744.
- [175] C. Ravinet Trillou, C. Delorge, C. Menet, M. Arnone, P. Soubrie, CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity, *Int. J. Obes. Relat. Metab. Disord.* 28 (2004) 640–648.
- [176] S.A. Robertson, G.M. Leininger, M.G. Myers Jr., Molecular and neural mediators of leptin action, *Physiol. Behav.* 94 (2008) 637–642.
- [177] Y. Rothmund, C. Preuschhof, G. Bohner, H.C. Bauknecht, R. Klingebiel, H. Flor, B.F. Klapp, Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals, *Neuroimage* 37 (2007) 410–421.
- [178] P. Rozin, E. Levine, C. Stoess, Chocolate craving and liking, *Appetite* 17 (1991) 199–212.
- [179] J.D. Salamone, A. Wisniecki, B.B. Carlson, M. Correa, Nucleus accumbens dopamine depletions make animals highly sensitive to high fixed ratio requirements but do not impair primary food reinforcement, *Neuroscience* 105 (2001) 863–870.
- [180] W. Schultz, P. Dayan, P.R. Montague, A neural substrate of prediction and reward, *Science* 275 (1997) 1593–1599.
- [181] A. Sclafani, Fat and sugar flavor preference and acceptance in C57BL/6J and 129 mice: experience attenuates strain differences, *Physiol. Behav.* 90 (2007) 602–611.
- [182] A. Sclafani, J.I. Glendinning, Flavor preferences conditioned in C57BL/6 mice by intragastric carbohydrate self-infusion, *Physiol. Behav.* 79 (2003) 783–788.
- [183] A. Sclafani, J.I. Glendinning, Sugar and fat conditioned flavor preferences in C57BL/6J and 129 mice: oral and postoral interactions, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 289 (2005) R712–R720.
- [184] A. Sclafani, L. Rinaman, R.R. Vollmer, J.A. Amico, Oxytocin knockout mice demonstrate enhanced intake of sweet and nonsweet carbohydrate solutions, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292 (2007) R1828–R1833.
- [185] M.M. Scott, J.L. Lachey, S.M. Sternson, C.E. Lee, C.F. Elias, J.M. Friedman, J.K. Elmquist, Leptin targets in the mouse brain, *J. Comp. Neurol.* 514 (2009) 518–532.
- [186] U. Shalev, J. Yap, Y. Shaham, Leptin attenuates acute food deprivation-induced relapse to heroin seeking, *J. Neurosci.* 21 (2001) RC129.
- [187] K.A. Sharkey, Q.J. Pittman, Central and peripheral signaling mechanisms involved in endocannabinoid regulation of feeding: a perspective on the munchies, *Sci STKE* 2005 (2005) pe15.
- [188] T. Shimbara, M.S. Mondal, T. Kawagoe, K. Toshinai, S. Koda, H. Yamaguchi, Y. Date, M. Nakazato, Central administration of ghrelin preferentially enhances fat ingestion, *Neurosci. Lett.* 369 (2004) 75–79.
- [189] G.E. Simon, M. Von Korff, K. Saunders, D.L. Miglioretti, P.K. Crane, G. van Belle, R.C. Kessler, Association between obesity and psychiatric disorders in the US adult population, *Arch. Gen. Psychiatry* 63 (2006) 824–830.
- [190] R. Sinha, D. Catapano, S. O'Malley, Stress-induced craving and stress response in cocaine dependent individuals, *Psychopharmacology (Berl.)* 142 (1999) 343–351.
- [191] K.P. Skibicka, C. Hansson, M. Alvarez-Crespo, P.A. Friberg, S.L. Dickson, Ghrelin directly targets the ventral tegmental area to increase food motivation, *Neuroscience* 180 (2011) 129–137.
- [192] D.M. Small, R.J. Zatorre, A. Dagher, A.C. Evans, M. Jones-Gotman, Changes in brain activity related to eating chocolate: from pleasure to aversion, *Brain* 124 (2001) 1720–1733.
- [193] D.M. Small, M. Jones-Gotman, A. Dagher, Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers, *Neuroimage* 19 (2003) 1709–1715.
- [194] K.S. Smith, K.C. Berridge, The ventral pallidum and hedonic reward: neurochemical maps of sucrose "liking" and food intake, *J. Neurosci.* 25 (2005) 8637–8649.
- [195] S.L. Smith, J.A. Harrold, G. Williams, Diet-induced obesity increases mu opioid receptor binding in specific regions of the rat brain, *Brain Res.* 953 (2002) 215–222.
- [196] T. South, X.F. Huang, High-fat diet exposure increases dopamine D2 receptor and decreases dopamine transporter receptor binding density in the nucleus accumbens and caudate putamen of mice, *Neurochem. Res.* 33 (2008) 598–605.
- [197] T. South, X.F. Huang, Temporal and site-specific brain alterations in CB1 receptor binding in high fat diet-induced obesity in C57BL/6 mice, *J. Neuroendocrinol.* 20 (2008) 1288–1294.
- [198] R. Spanagel, A. Herz, T.S. Shippenberg, The effects of opioid peptides on dopamine release in the nucleus accumbens: an in vivo microdialysis study, *J. Neurochem.* 55 (1990) 1734–1740.

- [199] R. Spanagel, A. Herz, T.S. Shippenberg, Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway, *Proc. Natl. Acad. Sci. USA* 89 (1992) 2046–2050.
- [200] R. Spangler, K.M. Wittkowski, N.L. Goddard, N.M. Avena, B.G. Hoebel, S.F. Leibowitz, Opiate-like effects of sugar on gene expression in reward areas of the rat brain, *Brain Res. Mol. Brain Res.* 124 (2004) 134–142.
- [201] E. Stice, S. Spoor, C. Bohon, D.M. Small, Relation between obesity and blunted striatal response to food is moderated by Taq1A A1 allele, *Science* 322 (2008) 449–452.
- [202] E. Stice, S. Spoor, C. Bohon, M.G. Veldhuizen, D.M. Small, Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study, *J. Abnorm. Psychol.* 117 (2008) 924–935.
- [203] E. Stice, S. Spoor, J. Ng, D.H. Zald, Relation of obesity to consummatory and anticipatory food reward, *Physiol. Behav.* 97 (2009) 551–560.
- [204] E. Stice, S. Yokum, K. Blum, C. Bohon, Weight gain is associated with reduced striatal response to palatable food, *J. Neurosci.* 30 (2010) 13105–13109.
- [205] S.L. Teegarden, T.L. Bale, Decreases in dietary preference produce increased emotionality and risk for dietary relapse, *Biol. Psychiatry* 61 (2007) 1021–1029.
- [206] S.L. Teegarden, E.J. Nestler, T.L. Bale, Delta FosB-mediated alterations in dopamine signaling are normalized by a palatable high-fat diet, *Biol. Psychiatry* 64 (2008) 941–950.
- [207] S.L. Teegarden, A.N. Scott, T.L. Bale, Early life exposure to a high fat diet promotes long-term changes in dietary preferences and central reward signaling, *Neuroscience* 162 (2009) 924–932.
- [208] D.L. Tempel, K.J. Leibowitz, S.F. Leibowitz, Effects of PVN galanin on macronutrient selection, *Peptides* 9 (1988) 309–314.
- [209] Z.D. Thornton-Jones, G.A. Kennett, K.R. Benwell, D.F. Revell, A. Misra, D.M. Sellwood, S.P. Vickers, P.G. Clifton, The cannabinoid CB1 receptor inverse agonist, rimonabant, modifies body weight and adiponectin function in diet-induced obese rats as a consequence of reduced food intake, *Pharmacol. Biochem. Behav.* 84 (2006) 353–359.
- [210] M. Tiggemann, E. Kemps, The phenomenology of food cravings: the role of mental imagery, *Appetite* 45 (2005) 305–313.
- [211] J. Turchan, W. Lason, B. Budziszewska, B. Przewlocka, Effects of single and repeated morphine administration on the prodynorphin, proenkephalin and dopamine D2 receptor gene expression in the mouse brain, *Neuropeptides* 31 (1997) 24–28.
- [212] S. Turkish, S.J. Cooper, Fluid consumption in water-deprived rats after administration of naloxone or quaternary naloxone, *Prog. Neuropsychopharmacol. Biol. Psychiatry* 7 (1983) 835–839.
- [213] Y.M. Ulrich-Lai, M.M. Ostrander, I.M. Thomas, B.A. Packard, A.R. Furay, C.M. Dolgas, D.C. Van Hooten, H.F. Figueiredo, N.K. Mueller, D.C. Choi, J.P. Herman, Daily limited access to sweetened drink attenuates hypothalamic-pituitary-adrenocortical axis stress responses, *Endocrinology* 148 (2007) 1823–1834.
- [214] Y.M. Ulrich-Lai, A.M. Christiansen, M.M. Ostrander, A.A. Jones, K.R. Jones, D.C. Choi, E.G. Krause, N.K. Evanson, A.R. Furay, J.F. Davis, M.B. Solomon, A.D. de Kloet, K.L. Tamashiro, R.R. Sakai, R.J. Seeley, S.C. Woods, J.P. Herman, Pleasurable behaviors reduce stress via brain reward pathways, *Proc. Natl. Acad. Sci. USA* 107 (2010) 20529–20534.
- [215] L.J. Vanderschuren, B.J. Everitt, Behavioral and neural mechanisms of compulsive drug seeking, *Eur. J. Pharmacol.* 526 (2005) 77–88.
- [216] V. Vialou, H. Cui, M. Perello, M. Mahgoub, H.G. Yu, A.J. Rush, H. Pranav, S. Jung, M. Yanguisawa, J.M. Zigman, J.K. Elmquist, E.J. Nestler, M. Lutter, A role for DeltaFosB in calorie restriction-induced metabolic changes, *Biol. Psychiatry* 70 (2011) 204–207.
- [217] D. Viganò, T. Rubino, G. Di Chiara, I. Ascari, P. Massi, D. Parolaro, Mu opioid receptor signaling in morphine sensitization, *Neuroscience* 117 (2003) 921–929.
- [218] N.D. Volkow, J.S. Fowler, G.J. Wang, R. Hitzemann, J. Logan, D.J. Schlyer, S.L. Dewey, A.P. Wolf, Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers, *Synapse* 14 (1993) 169–177.
- [219] N.D. Volkow, L. Chang, G.J. Wang, J.S. Fowler, Y.S. Ding, M. Sedler, J. Logan, D. Franceschi, J. Gatlery, R. Hitzemann, A. Gifford, C. Wong, N. Pappas, Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex, *Am. J. Psychiatry* 158 (2001) 2015–2021.
- [220] N.D. Volkow, J.S. Fowler, G.J. Wang, R. Baler, F. Telang, Imaging dopamine's role in drug abuse and addiction, *Neuropharmacology* 56 (Suppl. 1) (2008) 3–8.
- [221] N.D. Volkow, G.J. Wang, F. Telang, J.S. Fowler, R.Z. Goldstein, N. Alia-Klein, J. Logan, C. Wong, P.K. Thanos, Y. Ma, K. Pradhan, Inverse association between BMI and prefrontal metabolic activity in healthy adults, *Obesity (Silver Spring)* 17 (2009) 60–65.
- [222] N.D. Volkow, D. Tomasi, G.J. Wang, J.S. Fowler, F. Telang, R.Z. Goldstein, N. Alia-Klein, C. Wong, Reduced metabolism in brain “control networks” following cocaine-cues exposure in female cocaine abusers, *PLoS ONE* 6 (2011) e16573.
- [223] D.L. Wallace, V. Vialou, L. Rios, T.L. Carle-Florence, S. Chakravarty, A. Kumar, D.L. Graham, T.A. Green, A. Kirk, S.D. Iniguez, L.I. Perrotti, M. Barrot, R.J. DiLeone, E.J. Nestler, C.A. Bolanos-Guzman, The influence of DeltaFosB in the nucleus accumbens on natural reward-related behavior, *J. Neurosci.* 28 (2008) 10272–10277.
- [224] G.J. Wang, N.D. Volkow, J.S. Fowler, J. Logan, N.N. Abumrad, R.J. Hitzemann, N.S. Pappas, K. Pascani, Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal, *Neuropsychopharmacology* 16 (1997) 174–182.
- [225] G.J. Wang, N.D. Volkow, J. Logan, N.R. Pappas, C.T. Wong, W. Zhu, N. Netusil, J.S. Fowler, Brain dopamine and obesity, *Lancet* 357 (2001) 354–357.
- [226] L. Wang, I.M. Lee, J.E. Manson, J.E. Buring, H.D. Sesso, Alcohol consumption, weight gain, and risk of becoming overweight in middle-aged and older women, *Arch. Intern. Med.* 170 (2010) 453–461.
- [227] B. Wansink, From mindless eating to mindlessly eating better, *Physiol. Behav.* 100 (2010) 454–463.
- [228] B. Wansink, J. Kim, Bad popcorn in big buckets: portion size can influence intake as much as taste, *J. Nutr. Educ. Behav.* 37 (2005) 242–245.
- [229] B. Wansink, C.R. Payne, P. Chandon, Internal and external cues of meal cessation: the French paradox redux?, *Obesity (Silver Spring)* 15 (2007) 2920–2924.
- [230] A. Waters, A. Hill, G. Waller, Bulimics' responses to food cravings: is binge-eating a product of hunger or emotional state?, *Behav. Res. Ther.* 39 (2001) 877–886.
- [231] S. Wee, G.F. Koob, The role of the dynorphin-kappa opioid system in the reinforcing effects of drugs of abuse, *Psychopharmacology (Berl.)* 210 (2010) 121–135.
- [232] H.P. Weingarten, Conditioned cues elicit feeding in sated rats: a role for learning in meal initiation, *Science* 220 (1983) 431–433.
- [233] H.P. Weingarten, D. Elston, The phenomenology of food cravings, *Appetite* 15 (1990) 231–246.
- [234] H.P. Weingarten, D. Elston, Food cravings in a college population, *Appetite* 17 (1991) 167–175.
- [235] F. Weiss, Neurobiology of craving, conditioned reward and relapse, *Curr. Opin. Pharmacol.* 5 (2005) 9–19.
- [236] F. Weiss, L.H. Parsons, G. Schulteis, P. Hyttia, M.T. Lorang, F.E. Bloom, G.F. Koob, Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats, *J. Neurosci.* 16 (1996) 3474–3485.
- [237] C.C. Welch, E.M. Kim, M.K. Grace, C.J. Billington, A.S. Levine, Palatability-induced hyperphagia increases hypothalamic Dynorphin peptide and mRNA levels, *Brain Res.* 721 (1996) 126–131.
- [238] D.T. Weldon, E. O'Hare, J. Cleary, C.J. Billington, A.S. Levine, Effect of naloxone on intake of cornstarch, sucrose, and polycose diets in restricted and nonrestricted rats, *Am. J. Physiol.* 270 (1996) R1183–R1188.
- [239] P.J. Wellman, J.R. Naton, K.W. Davis, Impairment of acquisition of cocaine self-administration in rats maintained on a high-fat diet, *Pharmacol. Biochem. Behav.* 88 (2007) 89–93.
- [240] M.A. White, B.L. Whisenant, D.A. Williamson, F.L. Greenway, R.G. Netemeyer, Development and validation of the food-craving inventory, *Obes. Res.* 10 (2002) 107–114.
- [241] M.E. Wolf, The Bermuda Triangle of cocaine-induced neuroadaptations, *Trends Neurosci.* 33 (2010) 391–398.
- [242] M.E. Wolf, X. Sun, S. Mangiavacchi, S.Z. Chao, Psychomotor stimulants and neuronal plasticity, *Neuropharmacology* 47 (Suppl. 1) (2004) 61–79.
- [243] J. Wolffgramm, G. Galli, F. Thimm, A. Heyne, Animal models of addiction: models for therapeutic strategies?, *J. Neural Transm.* 107 (2000) 649–668.
- [244] J.E. Woods, P.F. McKay, J. Masters, R. Seyoum, A. Chen, L. La Duff, M.J. Lewis, H.L. June, Differential responding for brain stimulation reward and sucrose in high-alcohol-drinking (HAD) and low-alcohol-drinking (LAD) rats, *Alcohol. Clin. Exp. Res.* 27 (2003) 926–936.
- [245] R. Yirmiya, I. Lieblich, J.C. Liebeskind, Reduced saccharin preference in CXBK (opioid receptor-deficient) mice, *Brain Res.* 438 (1988) 339–342.
- [246] M. Zhang, A.E. Kelley, Opiate agonists microinjected into the nucleus accumbens enhance sucrose drinking in rats, *Psychopharmacology (Berl.)* 132 (1997) 350–360.
- [247] M. Zhang, B.A. Gosnell, A.E. Kelley, Intake of high-fat food is selectively enhanced by mu opioid receptor stimulation within the nucleus accumbens, *J. Pharmacol. Exp. Ther.* 285 (1998) 908–914.
- [248] D. Zhang, L. Zhang, D.W. Lou, Y. Nakabeppu, J. Zhang, M. Xu, The dopamine D1 receptor is a critical mediator for cocaine-induced gene expression, *J. Neurochem.* 82 (2002) 1453–1464.
- [249] M. Zhang, C. Balmadrid, A.E. Kelley, Nucleus accumbens opioid, GABAergic, and dopaminergic modulation of palatable food motivation: contrasting effects revealed by a progressive ratio study in the rat, *Behav. Neurosci.* 117 (2003) 202–211.
- [250] M. Ziotopoulou, C.S. Mantzoros, S.M. Hileman, J.S. Flier, Differential expression of hypothalamic neuropeptides in the early phase of diet-induced obesity in mice, *Am. J. Physiol. Endocrinol. Metab.* 279 (2000) E838–E845.