Common cellular and molecular mechanisms in obesity and drug addiction

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Abstract | The hedonic properties of food can stimulate feeding behaviour even when energy requirements have been met, contributing to weight gain and obesity. Similarly, the hedonic effects of drugs of abuse can motivate their excessive intake, culminating in addiction. Common brain substrates regulate the hedonic properties of palatable food and addictive drugs, and recent reports suggest that excessive consumption of food or drugs of abuse induces similar neuroadaptive responses in brain reward circuitries. Here, we review evidence suggesting that obesity and drug addiction may share common molecular, cellular and systems-level mechanisms.

Hyperphagia
Excessive consumption of food (above caloric requirements), which can reflect increased motivation to consume palatable food and/or deficits in brain circuitries that regulate satiety.

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One of the primary functions of the brain during periods of negative energy balance is to reprioritize behavioural output to procure and consume food, thereby replenishing energy stores that are depleted by caloric expenditure. Much is known about hypothalamic and hindbrain circuitries that control energy homeostasis and the hormonal regulators of hunger and satiety, such as leptin, ghrelin (also known as appetite-regulating hormone) and insulin, on these circuitries (FIG. 1). In addition to these homeostatic energy systems, reward systems also have key roles in regulating feeding behaviour. In particular, brain reward systems control learning about the hedonic properties of food, shifting attention and effort towards obtaining food rewards and regulating the incentive value of food or environmental stimuli that predict the availability of food rewards. Hormonal regulators of energy homeostasis can also act on brain reward circuits, most notably on the mesoaccumbens dopamine system[1], to increase or decrease the incentive value of food depending on energy requirements. However, electrical or chemical stimulation of brain areas that regulate food reward can trigger binge-like overeating even in recently fed animals in which homeostatic satiety signals have been engaged[2,3]. This suggests that obtaining the pleasurable effects of food is a powerful motivating force that can override homeostatic satiety signals, and in agreement with this, meals that consist of palatable food are generally consumed with greater frequency and in greater portion size than those consisting of less palatable food[4]. As a single meal of increased portion size can trigger increased food intake over several days[5], such hedonic overeating is likely to be an important contributor to weight gain and the development of obesity.

As common brain circuits regulate the hedonic properties of palatable food and drugs of abuse, and as there are striking phenomenological similarities between the overeating in obesity and excessive drug use in addiction, it is perhaps not surprising that these disorders have been proposed to share common underlying neurobiological mechanisms[1]. Nevertheless, it is important to point out that there is much ongoing debate about the idea that food can be 'addictive' in the same sense as drugs of abuse[6,7]. Here, we provide an overview of the brain systems that process information that is related to the hedonic properties and incentive value of palatable food, and discuss how addictive drugs can 'hijack' these systems. In addition, we highlight common cellular and molecular mechanisms in these circuitries that may contribute to both obesity and drug addiction.

Brain systems encoding food palatability

Genetic factors play a major part in regulating vulnerability to obesity, and levels of adiposity have been shown to be a highly heritable trait (BOX 1). In many cases, genes that are associated with excessive body weight contribute to obesity by increasing preference for palatable food. It is well established that palatable food that is rich in fat and refined sugars can provoke hyperphagia. Palatable high-fat food promotes larger meal sizes, less postprandial satiety and greater caloric intake than diets that are high in carbohydrates but low

in fat[8]. Hence, the perceived palatability of food contributes importantly to overconsumption and weight gain. The sensory characteristics of food, most notably its taste, smell, texture and appearance, have key roles in determining its palatability. The sensory information that is derived from the ingestion of palatable food is integrated in the primary and secondary gustatory cortices (FIG. 2). Chemosensory neurons in the oral cavity that are involved in tastant detection project to the nucleus tractus solitarius (NTS) in the brainstem[9]. The NTS in turn projects to the gustatory thalamus (ventroposteromedial (VPM) thalamic nucleus)[10], which innervates the primary gustatory cortex (PGC) in the insula and operculum[10]. As the name implies, the PGC is critically involved in processing information related to the taste of food and its hedonic valuation[11]. Afferents from the PGC project to a region of the the caudolateral orbitofrontal cortex (OFC) termed the secondary gustatory cortex (SGC). In addition to taste, other modalities of sensory input related to food palatability (for example, smell, sight and texture) also converge on the PGC and SGC[10]. The PGC and SGC project to the striatum, particularly the nucleus accumbens (NAc), thereby modifying neuronal activity in feeding-related striatohypothalamic and striatopallidal circuitries[1]. These striatal feeding circuits are in turn influenced by mesolimbic and nigrostriatal dopaminergic inputs[1]. It is well established that the striatum regulates consumption of both palatable food and drugs of abuse[1,12]. As described in detail below, recent evidence suggests that other components of the brain circuitry that are involved in processing food palatability — particularly the NTS, insula and OFC — also regulate the consumption of addictive drugs.

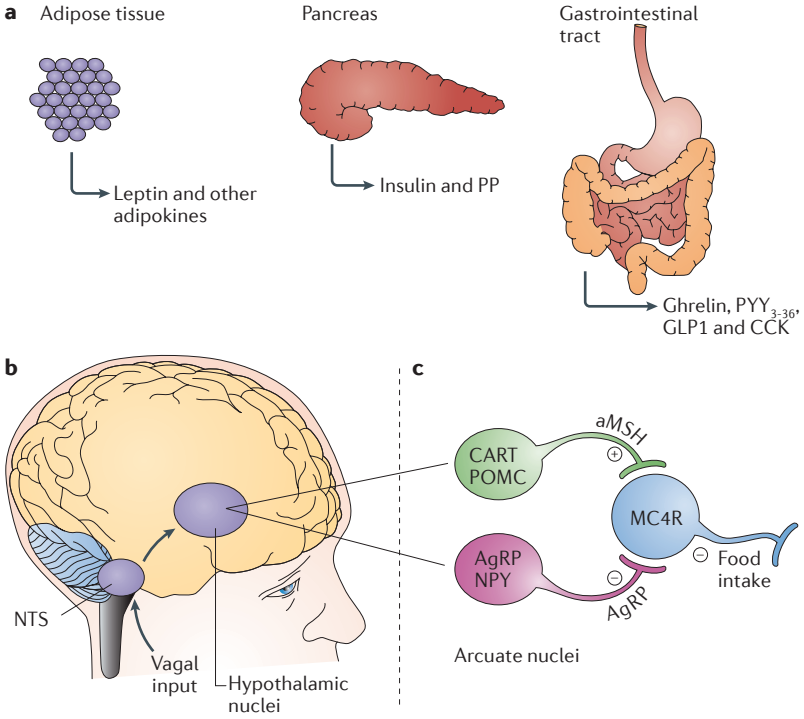

Figure 1 | **Overview of homeostatic feeding circuits. a** | Hormonal regulators of hunger, satiety and adiposity are released from the periphery. These include leptin and other adipokines, and also inflammatory cytokines, from adipose tissue. Insulin and pancreatic polypeptide (PP) are secreted from the pancreas. Furthermore, ghrelin (also known as appetite-regulating hormone), pancreatic peptide YY_{3-36} (PYY_{3-36}), glucagon-like peptide 1 (GLP1, a cleavage product of glucagon) and cholecystokinin (CCK) are released from the gastrointestinal tract. These hormonal regulators of energy balance act on hindbrain and hypothalamic brain sites to influence hunger and satiety. **b** | Hormonal signals from the viscera that regulate energy balance, and vagal nerve input that is related to stomach distention after meal ingestion, alter neuronal activity in the nucleus tractus solitarius (NTS). The NTS relays information related to energy balance to homeostatic feeding circuits in the hypothalamus. **c** | In the arcuate nucleus in the mediobasal hypothalamus, so-called first-order neurons that contain agouti-related peptide (AgRP) and neuropeptide Y (NPY) are activated by orexigenic signals and inhibit the so-called second-order neurons that express melanocortin 4 receptor (MC4R), and this tonically inhibits feeding behaviour. Conversely, anorexigenic signals activate first-order neurons containing cocaine- and amphetamine-regulated transcript (CART) and proopiomelanocortin (POMC), which stimulates the release of α-melanocyte-stimulating hormone (αMSH), a cleavage product of POMC. This results in the activation MC4R neurons and inhibition of feeding behaviour.

Nucleus tractus solitarius in food and drug reward

Neurons that produce catecholamine neurotransmitters are a major class within the NTS that is involved in regulating feeding behaviour (FIG. 3). The NTS receives information from chemosensory neurons in the oral cavity that process the taste of food, and ascending projections transmit this information to thalamic brain sites. In addition, NTS catecholamine neurons are activated by afferents from the gastrointestinal tract that signal meal ingestion or gastric distension, and by circulating satiety signals such as cholecystokinin (CCK)[13]. The NTS relays this visceral information to homeostatic feeding centres in the hypothalamus. Intriguingly, rats or mice that are maintained on a high-fat diet or mice that are genetically prone to develop obesity show decreased responsiveness of NTS catecholamine neurons to lipid ingestion[14,15]. This suggests that the hyperphagia that is associated with consumption of palatable high-fat food may be related to adaptive responses in the NTS, resulting in decreased sensitivity to gut hormones that signal satiety.

In addition to thalamic and hypothalamic feeding centres, NTS catecholaminergic neurons — specifically those in the A2 region of the NTS that produce noradrenaline — also project densely to limbic brain regions that are involved in stress and reward processing, including the shell region NAc, the central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST)[16] (FIG. 3). These same brain regions, collectively part of a larger contiguous cluster of functionally, structurally and chemically related brain structures termed the extended amygdala, have key roles in regulating the acute reinforcing properties of drugs of abuse and the development of drug dependence during chronic drug exposure[17] (see BOX 2 for a discussion of the role of stress in obesity and addiction). Intriguingly, nicotine that is applied to the tongue of rats excites gustatory neurons in the NTS and simultaneously decreases their responsiveness to a broad range of tastants[18]. This suggests that the actions of nicotine and other drugs of abuse on peripheral sensory systems converge on NTS neurons[19,20], or the direct actions of these drugs within the NTS, could contribute to their potential for abuse. Consistent with this possibility, the rewarding

Protracted drug abstinence
This is an aversive state that can persist in drug-dependent subjects long after cessation of drug use. Protracted abstinence is thought to increase vulnerability to relapse to drug-taking behaviour.

Reinforcer
This is a stimulus (object or event) that is obtained or that occurs in response to a particular behaviour and that is associated with an increased probability that the behavioural response that resulted in delivery of the stimulus will occur again. In essence, a reinforcer is anything that increases the likelihood that a given behaviour will be repeated.

properties of morphine are completely ablated in dopamine β-hydroxylase (DBH) knockout mice, which cannot synthesize noradrenaline[21]. However, virus-mediated re-expression of DBH in the NTS of the knockout mice re-established their sensitivity to morphine reward[21]. In addition to drug reward, the NTS also plays an important part in the development of drug dependence and the aversive consequences of drug withdrawal. NTS activity is increased in rats undergoing opiate withdrawal, resulting in higher levels of noradrenaline transmission in the extended amygdala[22], which contributes to the expression of aversive aspects of withdrawal[22]. Persistent activation of the NTS during periods of protracted drug abstinence in dependent rats also enhances sensitivity to the motivational properties of addictive drugs and increases vulnerability to stress-induced reinstatement of drug seeking behaviours (that is, relapse)[16]. The increased sensitivity to drug reward in rats undergoing periods of protracted abstinence is associated with decreased sensitivity to food reward[23]. As such, long-term alterations in NTS function may contribute to the enhanced motivational properties of addictive drugs and the diminished value of food and other natural reinforcers that are evident in drug-addicted individuals[23].

Insights are beginning to emerge into the molecular signalling events in the NTS that contribute to obesity and drug dependence. For example, the vagus nerve transmits information that is related to gastric distension to the NTS[24], and vagal nerve activation suppresses food intake in rats[25] and humans[26]. Human brain imaging studies have shown that an implantable device that triggers stomach expansion in response to vagal nerve stimulation increases metabolism in areas of the brain that are involved in food reward and palatability, including the OFC, striatum and hippocampus[27]. Intriguingly, bariatric surgery in overweight individuals can increase alcohol use[28]. These findings support the idea that the NTS influences activity in brain reward circuits and thereby regulates food and drug intake. In rats, repeated vagal nerve stimulation increases expression of the transcription factor ΔFOSB in NTS[29]. Similarly, the development of opiate dependence in rats is also associated with increased NTS expression of ΔFOSB[30]. ΔFOSB is a splice variant of the full-length FOSB gene product[31] and is known to accumulate in the striatum and other reward-related brain areas in rats and mice during chronic exposure to various classes of addictive drugs, and it persists long after drug exposure has ceased. Moreover, ΔFOSB increases the motivational properties of addictive drugs, probably by triggering structural and functional alterations in reward circuitries that increase their responsiveness to drugs and drug-associated stimuli[32]. Hence, it is possible that ΔFOSB signalling in the NTS could contribute to the development of obesity. In addition, ΔFOSB accumulation in the NTS could account for the simultaneous increase in sensitivity to drug reward and decrease in sensitivity to food reward, described above, in animals undergoing protracted abstinence from chronic drug exposure.

Nucleus tractus solitarius neuropeptides in drug reward. In addition to catecholaminergic neurons in the NTS, separate neuronal populations produce neuropeptides such as proopiomelanocortin (POMC) or glucagon-like peptide 1 (GLP1, a cleavage product of glucagon). In a similar way to noradrenaline-containing neurons, NTS POMC neurons are activated by vagal afferents from the gastrointestinal tract and circulating satiety signals, and they contribute to limiting food intake[33]. Enhancing POMC transmission in the NTS can induce weight loss and protect against diet-induced obesity[34]. Intriguingly, NTS infusion of opiates, which is known to increase food intake, inhibits POMC neurons[33], suggesting that these cells may play a part in opiate reward and dependence. GLP1 is primarily synthesized by intestinal L cells, and it serves to lower blood glucose levels and stimulate insulin secretion[35]. GLP1 is also produced by a small number of neurons in the NTS that inhibit food intake[36], particularly in response to gastric distention[37], stress and illness[38]. Disruption of GLP1 production in the NTS or GLP1 receptor signalling in the brain results in hyperphagia in rats[38], suggesting that overeating may induce deficits in central GLP1 receptor signalling that contribute to obesity. Activation of GLP1 receptors in the NTS probably decreases food intake through a mechanism involving protein kinase C (PKC)-mediated concurrent inhibition of AMP-activated protein kinase (AMPK) and stimulation of mitogen-activated protein kinase (MAPK) cascades[39]. So far, the roles of GLP1 receptors in the brain, and AMPK and MAPK in the NTS, in regulating drug reward and dependence have not been investigated.

Insular cortex in obesity and drug addiction

The insula and operculum primarily encode and store information related to the valence (appetitive or noxious) and magnitude of the hedonic properties of palatable food[1,10] (FIG. 2). In addition to its role in taste memory, the insula may also regulate the experience

Box 1 | Genetic and epigenetic factors that contribute to obesity

Familial forms of obesity have been identified in which null mutations in single genes implicated in homeostatic regulation of energy balance, such as those encoding leptin or the melanocortin 4 receptor (MC4R), can profoundly increase adiposity independent of the type of diet that is consumed. In addition, genome-wide association studies have identified single nucleotide polymorphisms that increase vulnerability to obesity in a polygenic manner. Polymorphisms in genes that are involved in energy balance often increase adiposity independently of the type of diet available[161]. However, in many cases genetic loci that are associated with body weight encode transcripts that increase risk of obesity by increasing preference for palatable food. This highlights the importance of hedonic brain systems in influencing propensity to overeat. Epigenetic mechanisms may also influence preference for palatable food and weight gain[162,163]. For example, consumption of a palatable high-fat diet increases DNA and histone methylation and decreases histone acetylation status in the promoter region of the opioid receptor mu 1 (*MOR1*) gene, which correlates with decreased MOR expression. Worryingly, chromatin remodelling in response to nutritional status *in utero* or during early postnatal development can affect dietary preference and metabolism, and thereby influence vulnerability to obesity later in life. Moreover, epigenetic alterations in gene expression, including genes that are expressed in brain reward circuitries that regulate the motivation to consume palatable food or drugs of abuse, can be transmitted across generations of offspring, resulting in trans-generational vulnerability to obesity and obesity-related diseases[162,164].

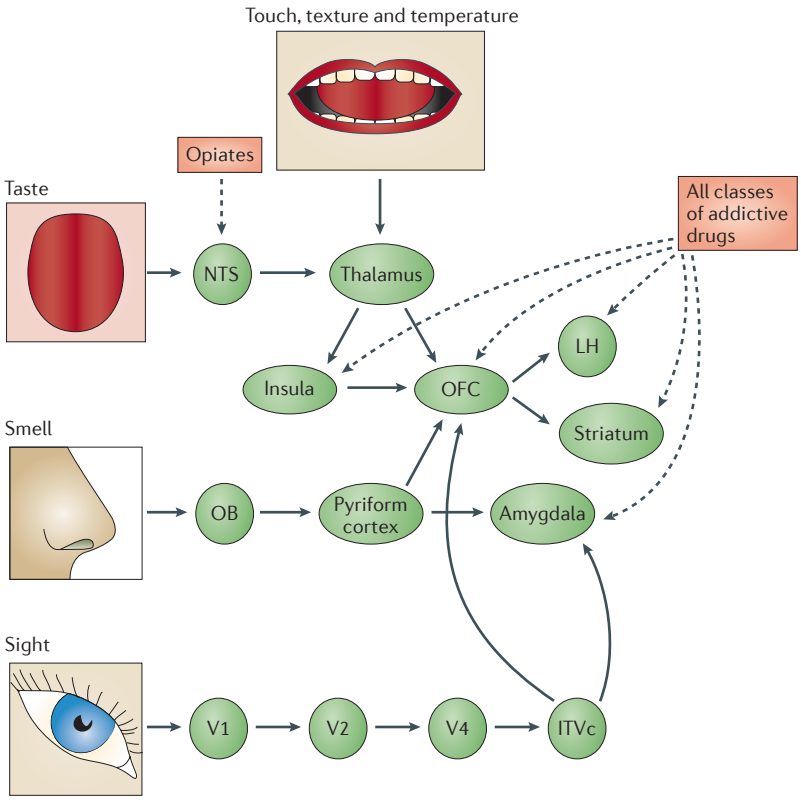

Figure 2 | **The neurocircuitry controlling palatable food and drug consumption.** The palatability of food is related to its touch and temperature, and is processed mainly by mechanoreceptors in the oral cavity that project to the gustatory thalamus. Texture also contributes to palatability, and may play an important part in detecting fat content in food. Taste plays a key part in food palatability, with chemoreceptors that detect tastants on the tongue projecting to the nucleus tractus solitarius (NTS). The smell of food is processed through the olfactory bulb (OB) and pyriform cortex. The appearance of palatable food is processed through the visual cortices (V1, V2 and V4) and then through the interior temporal visual cortex (ITVc). Information related to food palatability from these different modalities of sensory input converge on the amygdala, insular cortex and orbitofrontal cortex (OFC), and from there into feeding circuits in the striatum and lateral hypothalamus (LH). The sensory properties of drugs of abuse can activate the same brain systems as palatable food. Furthermore, drugs of abuse penetrate into the CNS and act directly in these brain systems. The sites of action of most major classes of addictive drugs on the neurocircuitory controlling food palatability are indicated (shown by dashed arrows). In addition, the NTS has a prominent role in regulating opiate reward and the development of dependence.

of conscious urges and cravings[40]. Humans or rodents with access to palatable food show a marked decrease in consumption when less palatable food than anticipated is made available, a phenomenon termed negative contrast[41,42]. This shift in preference towards the most hedonic food available, and the rejection of less palatable options, may play a key part in the development of obesity by contributing to persistent overconsumption of palatable energy-dense food[41,42]. Importantly, lesions to the insula abolish diet-associated negative contrast effects[43]. Similarly, a lesion to the gustatory thalamus, which is innervated by the NTS and in turn projects to the insula, also abolishes diet-associated negative contrast[44]. Obese human subjects show decreased functional connectivity strength in the insular cortex under resting conditions[45], perhaps reflecting diminished control over insular activation. Consistent with this interpretation, obese individuals show enhanced insular activation in response to palatable food[46]. Moreover, young adults who are at risk of developing obesity (both parents had a body mass index (BMI) score of ≥27) showed enhanced insula and operculum activation in response to monetary or food rewards compared with adolescents who have a low risk of developing obesity (both parents with a body mass index score of <25)[47]. This suggests that innately enhanced responsiveness of the insula, which may contribute to increased sensitivity to the taste of palatable food and a shift in dietary preference towards such food, increases vulnerability to obesity[1].

In addition to its role in taste memory and food preference, the insula also plays a key part in drug addiction. Abstinence-induced cigarette craving in smokers is highly correlated with activation of the insular cortex[48]. More notably, stroke-related damage to the insula in human smokers can result in a disruption of tobacco addiction, characterized by spontaneous cessation of the smoking habit and a low urge to smoke thereafter[49]. In rats, chemical inactivation of the insula, or disruption of hypocretin receptor type 1 (also known as orexin receptor type 1) signalling in this structure, decreases intravenous nicotine self-administration behaviour[50] and amphetamine-seeking behaviour[51]. Within insular neurons, cocaine treatment[52] or exposure to environmental cues that predict availability of palatable food[53] increase expression of the immediate early gene and transcriptional regulator early growth response protein 1 (also known as transcription factor ZIF268), which plays a key part in neuronal plasticity and long-term memory formation. This suggests that palatable food and drugs of abuse can induce similar adaptive responses in the insular cortex. Mice that are permitted to consume highly palatable food show a marked increased in MAPK signalling in the insular cortex[54]. Moreover, this increase in insular MAPK signalling, perhaps as a consequence of NMDA and metabotropic glutamate 5 receptor activation[55], controls the induction of a long-term taste memory[56]. Little is known about the effects of drugs of abuse on MAPK signalling in the insula and its involvement in drug-seeking behaviours.

Orbitofrontal cortex in obesity and addiction

In contrast to the insula, which encodes information related to the valence and magnitude of the hedonic properties of food, the OFC seems to continuously update information related to the relative motivational value of palatable food, based on information from metabolic or hedonic circuitries in the brain[57]. As such, the OFC probably plays a key part in the development of sensory-specific satiety during meals based on the diminished incentive value of any given food item, independent of changes in the perception of its palatability[57]. In a recent study, volunteers who were asked to imagine repeatedly eating a particular type of desirable food (chocolate or cheese) subsequently consumed far less of that food when it was actually available compared with the amounts eaten by individuals who imagined eating less of the food, those who envisioned eating a different

type of palatable food or those who did not consider the food at all[58]. The decreased food consumption was not related to changes in subjective hedonic value, the participants simply desired it less (that is, they experienced sensory-specific satiety following imagined consumption)[58]. These findings show how readily the incentive value of food can be dissociated from its absolute hedonic properties[58], and they show the importance of higher-order cortical brain centres that are involved in mental representations in attributing the relative motivational value of any given food item. Considering the key role of the OFC in attributing value to food[59], these and related findings suggest that disruption of OFC function could result in inappropriate attribution of incentive value to food, resulting in weight gain[60]. Consistent with this possibility, obesity in humans is associated with marked deficits in OFC metabolism[60]. Furthermore, frontotemporal dementia resulting in atrophy of the OFC and insula triggers the emergence of binge-like overeating of palatable food in humans[61]. Recently, it was shown that activation of mu opioid receptors in the OFC induces hyperphagia in rats[62]. This suggests that local opioid receptor transmission in the OFC[62], which could influence the activity of downstream feeding circuits in the striatum (see below), controls feeding behaviour.

The OFC may also play a key part in attributing motivation value to cocaine and other drugs of abuse.

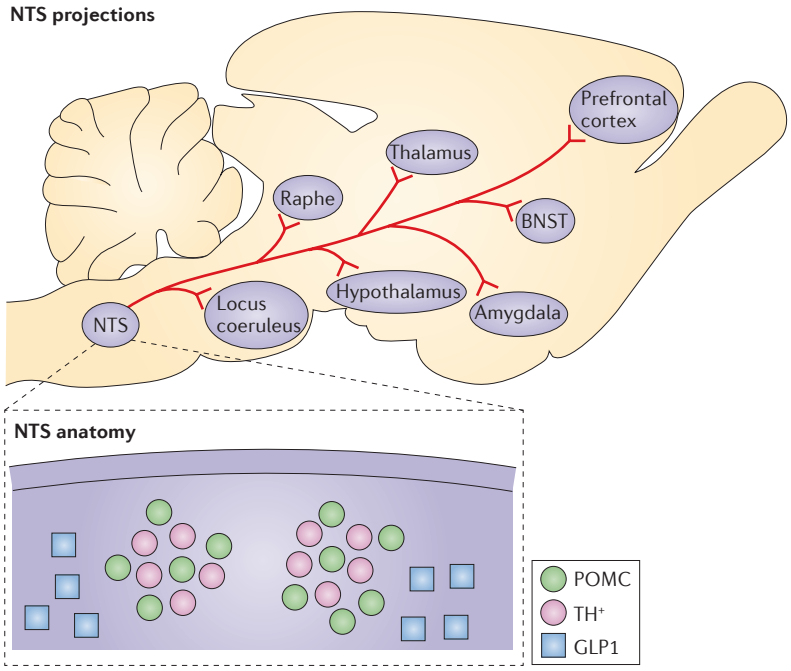

Figure 3 | **The nucleus tractus solitarius in food and drug consumption.** The nucleus tractus solitarius (NTS) receives input from the gastrointestinal tract from the vagal nerve, and in turn projects to midbrain, thalamic, hypothalamic, limbic and cortical brain regions that are involved in processing food palatability, hedonic aspects of food and drugs of abuse, and the effects of stress on food and drug consumption. The NTS expresses different populations of neurons that are involved in regulating food and drug intake, including catecholaminergic neurons that express the enzyme tyrosine hydroxylase (TH^+), those that express proopiomelanocortin (POMC) and those that express glucagon-like peptide 1 (GLP1, a cleavage product of glucagon). BNST, bed nucleus of the stria terminalis.

Chemical inactivation of the OFC rendered rats insensitive to alterations in the relative reinforcing value of different unit doses of cocaine that were available for intravenous self-administration[63]. Lesions of the OFC also block the ability of drug-paired environmental cues that predict palatable food or drug availability to drive seeking behaviours[64,65], perhaps by disrupting the attribution of salience to the food- or drug-paired cues[66]. A history of intravenous cocaine self-administration behaviour in rats, or repeated exposure to amphetamine, induces structural and functional alterations in the OFC of rats that correlated with deficits in OFC-dependent cognitive performance[67,68]. Based on these and similar findings, it has been proposed that drug-induced remodelling of the OFC may contribute to the transition from controlled to uncontrolled drug use in addiction[67,69]. The underlying molecular mechanisms that contribute to OFC dysfunction are beginning to emerge. In rats, volitional consumption of cocaine or alcohol increases the expression of the transcription factor ΔFOSB in the OFC[70]. This increase in ΔFOSB expression in OFC exacerbates the increase in impulsive-like behaviour that is observed during withdrawal from chronic cocaine self-administration[71]. As increases in impulsive choice are thought to increase vulnerability to addiction, drug-induced increases in ΔFOSB in the OFC may drive the development of addiction. It will therefore be important to determine whether overconsumption of palatable food similarly increases ΔFOSB expression in the OFC, and whether this influences vulnerability to obesity.

Mesostriatal system in obesity and addiction

Information relating to the sensory properties of palatable food, which is processed in the OFC and other cortical structures, is transmitted to feeding-related circuits in the striatum, particularly to so-called 'hedonic hot spots' in the shell region of the NAc. Hedonic hot spots in accumbens project to, and control the activity of, lateral hypothalamic and pallidal brain sites. These striatohypothalamic and striatopallidal systems, which are regulated locally by opioid and endocannabinoid signalling and also by dopamine transmission arising from mesoaccumbens and nigrostriatal input, control responsiveness to environmental stimuli that predict food availability and palatability, approach behaviours and attribution of incentive value to palatable food[1].

In addition to the sensory properties of palatable food, the striatum also plays an important part in responding to the post-ingestive effects of food metabolism[72]. Specifically, the release of macronutrients from energy-dense food can activate metabolic signalling pathways in the viscera and thereby stimulate dopamine inputs onto feeding circuits in the striatum, independently of the sensory properties of the food[73,74]. The functional transient receptor potential channel subfamily M member 5 (TRPM5) is necessary for detecting sweet, bitter and amino acid (umami) tastants[75]. Taste-blind *Trpm5* knockout mice do not show a preference for sucrose over water when presented briefly with a choice between both solutions[73,74], confirming their inability to detect sweet-tasting solutions. However, when the *Trpm5* knockout

Box 2 | **The role of stress in obesity and addiction**

Stress triggers intense bouts of feeding, particularly of palatable food, in rodents, monkeys and humans, with palatable food consumption thought to attenuate the aversive effects of stress[84,165]. Obesity is associated with elevated stress-related glucocorticoid secretion, suggesting that stress and obesity are closely intertwined. Indeed, 'withdrawal' from the palatable diet increases expression of stress hormone corticotropin-releasing factor (CRF) in the central nucleus of the amygdala of rats and mice, which may drive the emergence of compulsive-like eating in rodents[84,166]. Amygdalar CRF levels are also increased in rats during withdrawal from all major drugs of abuse, an effect that has been suggested to drive compulsive drug seeking[167].

Similar to obesity, hunger is a stressor in humans, monkeys and rodents, with food restriction increasing the subjective motivation to eat in response to stress in humans[168]. Furthermore, rats undergoing cyclic periods of caloric restriction and re-feeding, which sensitizes rats to stress-induced overeating, demonstrate compulsive-like consumption of palatable food[169,170]. Hence, increased activity of stress pathways in response to overeating and weight gain on the one hand, or food restriction and hunger on the other, may contribute to the development of overeating and weight gain through similar stress-related mechanisms that drive the development of drug addiction.

mice were repeatedly allowed longer access to water or sucrose dilutions at discrete locations in the testing environment, and therefore able to associate post-ingestive effects of water or sucrose with their consummatory behaviour, they showed a clear preference for the sucrose solutions. Importantly, the *Trpm5* knockout mice did not develop a preference for the non-caloric sweetener sucralose under the same test conditions, demonstrating that the post-ingestive caloric effects of sucrose were responsible for the increased preference for sucrose in the knockout mice[73,74]. Sucrose increased dopamine levels in the NAc and dorsal striatum of the *Trpm5* mice[73,74], suggesting that non-gustatory metabolic signals in the knockout mice were sufficient to stimulate midbrain dopamine neurons that drive preference for calorically dense solutions. Intriguingly, *Trpm5* channels on the tongue also regulate taste responses to nicotine and alcohol, and contribute to their volitional consumption[76,77]. This suggests that, in addition to their direct actions in the brain, sensory information that is related to inhaled or orally consumed drugs of abuse contributes to their intake.

Signalling events downstream of dopamine receptors. Palatable food or drugs of abuse, and environmental cues that predict their delivery, increase dopamine transmission in the striatum, thereby influencing striatohypothalamic and striatopallidal circuitries that control the hedonic and incentive properties of food and abused drugs[1]. The roles of striatal dopamine transmission in obesity, including the contributions of constitutive and diet-induced alterations in dopamine receptor function, has been reviewed in detail elsewhere[1,12,78]. Here, the focus will be on emerging evidence suggesting that drugs of abuse and palatable food converge on common intracellular signalling cascades in the striatum and in midbrain dopamine neurons that project to the striatum, which contribute to drug addiction and obesity (FIG. 4). Cocaine and other drugs of abuse increase the expression of ΔFOSB throughout the striatum, particularly in the D1 dopamine receptor and dynorphin-expressing medium spiny neurons of the direct pathway[79]. Moreover, gradual accumulation of ΔFOSB in the striatum in response to drug consumption increases their motivation properties, which is thought to contribute to the development of drug addiction[80]. Interestingly, mice that were exposed to a high-fat diet during early postnatal development (postnatal days 21–28) for 1 week had increased preference for dietary fat intake in adulthood[81], and this increased preference for calorically dense food was associated with alterations in intracellular molecular transducers of dopamine receptor signalling[81]. In particular, ΔFOSB levels were increased in the NAc of these mice[81]. Similarly, increased ΔFOSB expression in the striatum was detected in adult mice that were permitted to eat palatable high-fat or sucrose diets[82–84], and this effect was associated with enhanced motivation to consume palatable diets. Furthermore, mice with restricted access to food, and that were therefore hungry and highly motivated to consume food, also showed increased striatal ΔFOSB expression[85].

Transgenic overexpression of ΔFOSB in the striatum, specifically in neurons of the direct pathway, resulted in greater responses for food rewards under fixed and progressive ratio schedules of reinforcement, suggesting that ΔFOSB increases the motivational properties of food[86]. These findings are strikingly similar to the enhanced responses to cocaine under fixed and progressive ratio reinforcement schedules that are induced by striatal overexpression of ΔFOSB[87]. Consumption of a palatable high-fat diet can normalize many of the deficits in dopamine receptor-associated signalling cascades in the striatum of ΔFOSB-overexpressing mice[88]. These deficits include decreases in the transcription factor cyclic AMP-responsive element binding protein (CREB), protein phosphatase 1 regulatory subunit 1B (DARPP32) and brain-derived neurotrophic factor (BDNF)[88]. In addition, markers of dopamine production and release, particularly tyrosine hydroxylase, the rate-limiting enzyme in the production of dopamine, and the dopamine transporter protein (DAT) were decreased in the ventral tegmental area (VTA)–striatum axis of the ΔFOSB-overexpressing mice[88], suggesting that ΔFOSB-overexpressing mice have decreased dopamine production in midbrain systems and decreased dopamine release into the striatum. Evidence of disrupted striatal dopamine transmission in ΔFOSB-overexpressing mice was ameliorated by access to a high-fat diet for 6 weeks[88]. This suggests that the palatable food may have increased motivational value in these mice because it can normalize deficits in dopamine signalling. Taken together, these data strongly suggest that striatal ΔFOSB signalling controls the motivational properties of food and drugs of abuse. It is important to note, however, that weight gain is similar in wild-type and ΔFOSB-overexpressing mice with access to standard chow or a high-fat diet[88]. It is therefore an intriguing possibility that caloric usage or other aspects of metabolism may be increased in ΔFOSB-overexpressing mice to compensate for their increased motivation to seek food, a possibility that has not yet been tested.

Direct pathway
The direct striatal pathway comprises medium spiny neurons (MSNs) that express dopamine D1 receptors and project directly to the globus pallidus interna (GPi). The indirect pathway comprises MSNs that express dopamine D2 receptors and project to the GPi indirectly through a pathway involving the globus pallidus externa (GPe) and the subthalamic nucleus.

Fixed and progressive ratio schedules
A fixed ratio schedule of reinforcement requires an animal to emit a fixed number of responses to earn a reinforcer. A progressive ratio schedule involves the animal emitting progressively greater numbers of responses to earn each subsequent reinforcer.

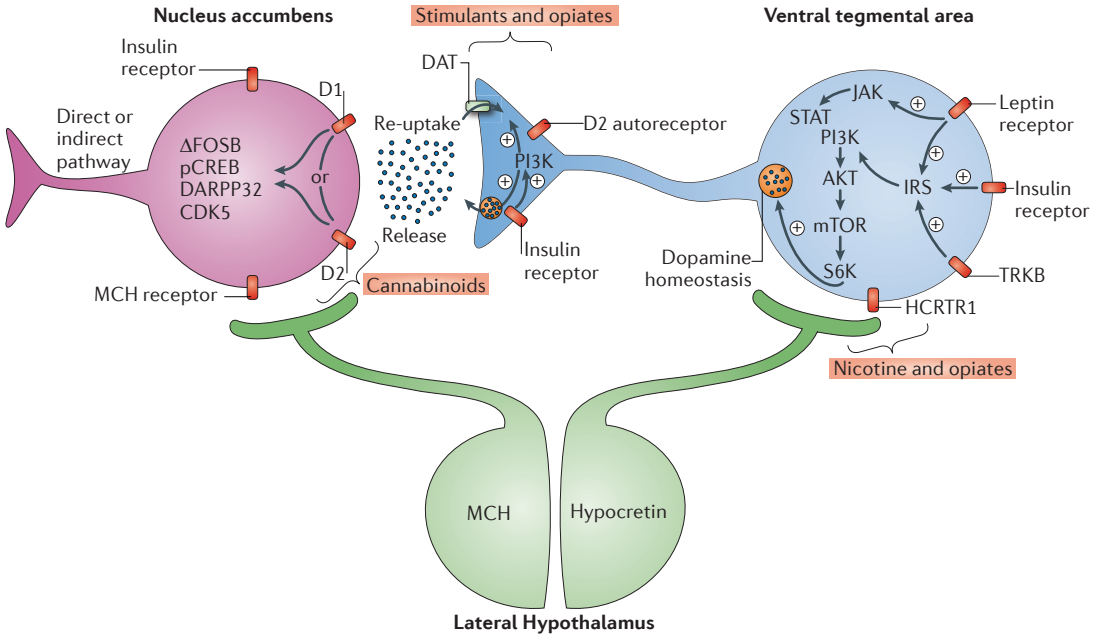

Figure 4 | **Intracellular signalling cascades in the striatum and mesoaccumbens dopamine pathway that regulate food intake and drug use.** The receptors for leptin, insulin and brain-derived neurotrophic factor (TRKB) are expressed on ventral tegmental area (VTA) dopamine neurons, where they regulate the phosphinositide 3-kinase (PI3K)–serine/threonine kinase AKT–mammalian target of rapamycin (mTOR) signalling cascade. Leptin can also regulate the JAK–STAT (Janus kinase–signal transducer and activator of transcription) signalling pathway. Leptin, insulin and BDNF signalling are necessary to maintain dopamine homeostasis, probably through actions involving the PI3K signalling cascade. Drugs of abuse like cocaine can also potentiate PI3K–AKT–mTOR signalling in midbrain dopamine neurons. Insulin receptors are also probably expressed presynaptically on dopamine terminals in the nucleus accumbens, and postsynaptically on medium spiny neurons, that express either dopamine D1 or D2 receptors, the so-called direct and indirect pathway neurons, respectively. Insulin receptors in the accumbens promote dopamine release and enhance the activity of the dopamine transporter (DAT), and thereby play an important part in accumbal dopamine homeostasis. This action probably contributes to the satiety-related actions of insulin and its ability to decrease palatable food intake. Conversely, all major drugs of abuse stimulate dopamine release into the accumbens, an action that is considered critical to their motivational properties. Dopamine signalling in the accumbens modulates the activity of ΔFOSB, cyclic AMP-responsive element binding protein (CREB), protein phosphatase 1 regulatory subunit 1B (DARPP32) and cyclin-dependent kinase 5 (CDK5) signalling pathways in medium spiny neurons, and thereby influences the motivational properties of food and addictive drugs. Neuropeptides that are produced in the lateral hypothalamus (LH) can also modulate the activity of VTA dopamine and striatal neurons. LH neurons that produce hypocretin (also known as orexin), project to the VTA and regulate VTA dopamine neurons and their responsiveness to palatable food and addictive drugs. LH neurons that produce melanin-concentrating hormone (MCH) project to the accumbens and control the motivational properties of food and addictive drugs, and also the responsiveness of medium spiny neurons, through MCH receptors expressed in this area. The main sites of action of most major classes of addictive drugs are indicated (shown by red boxes). IRS, insulin receptor substrate; HCRTR1, hypocretin receptor type 1; S6K, ribosomal protein S6 kinase β1.

Other components of dopamine receptor signalling in the striatum also regulate the motivational properties of both drugs of abuse and food. For example, expression of cyclin-dependent kinase 5 (CDK5) in the striatum is regulated by ΔFOSB and cocaine[89,90]. Pharmacological or genetic disruption of CDK5 signalling in striatum increases cocaine reward in mice[91,92]. This suggests that drug-induced increases in CDK5 expression in striatum may be an adaptive response in brain reward circuits to counter the effects of cocaine and thereby protect against addiction[93]. Disruption of CDK5 signalling in the brain also increases the incentive motivational properties of food[92], suggesting again that common biochemical mechanisms in the striatum regulate the motivational properties of addictive drugs and food. Lastly, activation of D1 dopamine receptor signalling in the striatum is known to cause the dephosphorylation of DARPP32 at serine residue 97. Replacement of serine 97 with an alanine reside, thereby preventing the phosphorylation-mediated regulation of DARPP32 through this site, results in profound decreases in sensitivity to the motivational properties of cocaine and food rewards[94]. Taken together, these observations provide compelling evidence that similar dopamine-activated signalling cascades in the striatum control the motivational properties of drugs of abuse and food, and that disruption of these cascades may contribute to the development of obesity or addiction.

Neuropeptide and hormonal signalling

In addition to downstream signalling events that are related to dopamine receptor activation, palatable food

and drugs of abuse can trigger neuroplasticity in striatal feeding circuits through hormonal and neuropeptide regulators of energy balance. Two major neuropeptides that are produced in the lateral hypothalamus and that are known to modulate striatal feeding circuits and dopamine input to these pathways, are melanin-concentrating hormone (MCH) and hypocretin (also known as orexin). MCH and hypocretin are produced in the lateral hypothalamus[95] — a brain region that is involved in regulating both feeding behaviour and reward processing — and increases in MCH or hypocretin signalling stimulate feeding behaviour[96,97]. Interestingly, genetic ablation of hypocretin neurons in the lateral hypothalamus leads to overeating, weight gain and obesity in mice[98], suggesting that hypocretin transmission plays a complex part in regulating food intake and weight gain. MCH receptors are expressed in the NAc, with activation of these receptors stimulating feeding behaviour[99] and inhibiting NAc neuronal firing[100]. These effects are likely to involve a decrease in adenylyl cyclase activity, and the consequent reductions in CREB activity, and reduced surface expression of the AMPA glutamate receptor subunit 1 (GluR1)[100]. Disruption of MCH receptor signalling in the NAc blocks the stimulant and conditioned reward effects of cocaine in mice[101]. Furthermore, ablation of MCH receptor signalling in the NAc also decreases intravenous cocaine self-administration and blocks relapse-like behaviour[101]. Hypocretin-containing neurons project from the lateral hypothalamus to the VTA, where hypocretin receptor type 1 (HCRTR1; also known as orexin receptor type 1) plays a key part in regulating mesolimbic dopamine transmission and the rewarding properties of various drugs of abuse and food, probably through regulation of PKC-dependent signalling cascades[102–104]. In summary, feeding-related neuropeptides, like MCH and hypocretin, have key roles in controlling food intake and drug use through modification of reward system activity, and probably contribute to the development of obesity and addiction.

Leptin signalling in the ventral tegmental area. In addition to hypothalamic neuropeptides, hormonal regulators of appetite that are produced in the viscera can modulate brain reward function. For example, ghrelin, which is produced in the stomach and pancreas, can increase appetite and food intake. Ghrelin acts partly by stimulating midbrain dopamine transmission and thereby increasing motivation for food or drugs of abuse[105]. Another major hormonal regulator of energy balance that modulates brain reward activity is leptin. Congenital leptin deficiency results in increased striatal activation in response to images of food[106], and leptin replacement therapy attenuates striatal activation of self-reported liking of food in these individuals[106]. Leptin can modulate striatal responses to food by controlling mesolimbic dopamine pathways. Leptin receptors are expressed on midbrain dopamine neurons[107–109], and leptin infusion into the VTA inhibits the activity of dopamine neurons[109], decreases food intake[109–111] and induces generalized decreases in sensitivity to reward in rats[111]. Conversely, knockdown of leptin receptors in the VTA in rats increases preference for palatable food[109] and enhances the motivational properties of food[112]. In hypothalamic circuitries, the JAK–STAT (Janus kinase–signal transducer and activator of transcription) cascade is a major pathway through which leptin signals its anorexigenic effects[113]. Infusion of leptin into the VTA, at doses that decrease feeding behaviour, activates the JAK–STAT cascade[109,110], and inhibition of JAK–STAT signalling in the VTA attenuates the anorexigenic effects of leptin[110]. Chronic cocaine treatment has been shown potentiate JAK–STAT signalling in the VTA[114]. It has therefore been proposed that cocaine-induced amplification of JAK–STAT signalling in the VTA may contribute to the long-lasting adaptations in brain reward circuitries that underlie cocaine addiction. In addition, by acting in a leptin-like manner, it is possible that cocaine-induced increases in JAK–STAT signalling in the VTA may contribute to the anorexigenic properties of the drug.

Insulin signalling in the ventral tegmental area. Insulin is another hormonal regulator of energy balance that can influence food intake by modulating striatal feeding circuits and midbrain dopamine input onto these circuits. Insulin activates the insulin receptor and a signalling cascade that involves insulin receptor substrate (IRS)-mediated activation of phosphoinositide 3-kinase (PI3K). PI3K subsequently activates tyrosine-protein kinase BTK (also known as ATK), which then activates mammalian target of rapamycin (mTOR) and its downstream effector ribosomal protein S6 kinase β1 (S6K1). Insulin receptors are expressed in the striatum[115] and on midbrain dopamine neurons[107]. Infusion of insulin into the VTA decreases food intake in rats[111,116], and conversely, selective deletion of insulin receptors in midbrain dopamine neurons in mice results in hyperphagia and increased weight gain compared with control mice[117]. These effects are related to a loss of insulin-stimulated PI3K signalling in dopamine neurons[117]. Diabetic rats have greatly diminished levels of dopamine in midbrain and striatal brain sites and are less sensitive to the rewarding properties of methamphetamine than control rats with physiological levels of insulin[118,119], demonstrating that insulin signalling is necessary to maintain dopamine transmission. These data suggest that acute activation of insulin receptors in the VTA can decrease the activity of dopamine-containing neurons in this brain site. However, insulin seems to act in a neurotrophic manner in the VTA as disruption of insulin signalling results in deficits in dopamine transmission.

Disruption of BDNF expression throughout the forebrain, or specifically in the VTA, results in hyperphagia and weight gain in mice, particularly when permitted access to a palatable high-fat diet[120], similar to the effects of knocking out insulin receptors in the VTA. Moreover, central depletion of BDNF is associated with a profound deficit in dopamine signalling in the NAc, suggesting that, like insulin, BDNF is essential to maintain appropriate levels of mesolimbic dopamine signalling[120]. Intriguingly, in addition to the acute inhibitory effects of leptin on VTA dopamine-containing neurons and the feeding behaviour that

Anorexigenic
A stimulus (object or event) that decreases appetite and food consumption.

are described above[109,121], hyperphagic *ob/ob* mice, in which leptin signalling is disrupted, have lower levels of tyrosine hydroxylase in midbrain dopamine neurons, a key enzyme in the biosynthesis of dopamine[108]. *ob/ob* mice also have reduced evoked dopamine release into the NAc[108] and decreased somatodendritic vesicular stores of dopamine in the VTA[122]. These deficiencies in dopamine signalling are normalized by treatment with exogenous leptin[108]. Together, these findings suggest that insulin, BDNF and leptin, which can all signal through the PI3K–serine/threonine kinase AKT–mTOR cascade, are necessary for appropriate dopamine production and signal transmission. Deficits in their actions disrupt the mesoaccumbens dopamine system and increase the animal's propensity to over-consume palatable high-fat food and develop obesity. In contrast to the motivational properties of palatable food and weight gain in mice with disrupted insulin, BDNF or leptin signalling in the VTA, these mice show diminished sensitivity to the motivational and psychomotor stimulant effects of cocaine and amphetamine[108,117]. Furthermore, disruption of the PI3K–AKT–mTOR signalling cascade in the VTA, achieved through virus-mediated expression of a dominant negative insulin receptor substrate 2 (IRS2) protein, attenuates the rewarding properties of cocaine and morphine in mice[123,124]. Thus, it is possible that disruption of insulin, BDNF and leptin signalling in the VTA not only increases propensity to become obese, which may reflect hedonic overeating to overcome a negative affective state associated with disrupted midbrain dopamine signalling[1], but also decreases sensitivity to the rewarding properties of addictive drugs like cocaine or morphine.

Insulin signalling in the striatum. Insulin increases DAT expression and function in the striatum through the canonical IRS–PI3K pathway[125]. Moreover, insulin potentiates the inhibitory effects of cocaine on dopamine release from striatal slices, an effect that is blocked by inhibition of PI3K[125]. Intriguingly, direct infusion of insulin into the NAc exacerbates the emergence of impulsive-like behaviour in rats that are treated with cocaine[125], as measured in a five-choice serial reaction time task. High levels of impulsivity in this task are known to predict vulnerability to develop compulsive-like cocaine seeking behaviours in rats[126], and humans with constitutively high levels of impulsivity are at increased risk of developing drug addiction or obesity[127]. Hence, insulin signalling locally in the striatum may influence vulnerability to addiction through the IRS–PI3K–AKT–mTOR cascade. The idea that the PI3K-AKT-mTOR cascade has a role in addiction is also supported by the finding that pharmacological inhibition of mTOR signalling using rapamycin, particularly in the NAc, decreases the motivational properties of cocaine in rats and mice[128]. Lastly, the PI3K–AKT–mTOR pathway is known to play an important part in long-term depression (LTD)[129], the process by which synaptic strength between neurons is enduringly decreased. Striatal LTD also depends on endocannabinoid and metabotropic glutamate receptor signalling and the transient receptor potential cation channel subfamily V member 1 (TRPV1) channel, all of which are known to regulate the rewarding properties of addictive drugs and the motivation to consume palatable food. Intriguingly, withdrawal from cocaine self-administration can induce deficits in the induction of LTD in the striatum[130] and concomitant decreases in striatal expression of core components of the PI3K–AKT–mTOR signalling cascade[131]. This deficit in LTD gradually recovers during extended periods of abstinence from cocaine self-administration behaviour in rats[130]. However, failure to recover striatal LTD after a period of extended access to cocaine is associated with the emergence of addiction-like behaviours[130]. Finally, so-called western diets, which are rich in refined sugars and fat, are deficient in omega 3 fatty acids, and as a result obese individuals are very often deficient in this essential nutrient[132]. Omega 3 deficiency in mice induces a striking deficit in LTD in the striatum[132], suggesting that striatal LTD deficits that result from dietary deficiencies may contribute to the development of drug addiction and obesity.

Inflammation in obesity and drug addiction

Emerging evidence suggests that induction of PI3K–AKT–mTOR-dependent LTD in brain is critically dependent on caspase 3, a signalling molecule that is involved in inflammation and apoptosis. Specifically, activation of NMDA receptors in response to synaptic activity increases intracellular calcium levels, which activates the calcium-dependent phosphatase calcineurin[133]. This in turn increases the release of cytochrome *c* from mitochondria through a mechanism that is dependent on the pro-apoptotic factors BCL-XL (BCL2 antagonist of cell death), XIAP (baculoviral IAP repeat-containing protein 4) and the apoptosis regulator BAX[133,134]. Cytochrome *c* in turn activates caspase 3, which then regulates the surface expression of AMPA receptor subunits and induces LTD through the AKT pathway[133,134]. Importantly, caspase 3 plays a key part in inflammatory signalling in the brain, including striatal and midbrain dopamine sites[135,136], suggesting that inflammatory pathways in the brain could also contribute to drug addiction and obesity.

Nuclear factor-κB signalling in obesity and addiction. Initiation of inflammatory signalling cascades triggers activation of nuclear factor-κB (NF-κB), a transcription factor that increases the transcription of proinflammatory cytokines and other genes that are involved in cellular responses to damage, infection and stress (FIG. 5). Adipocytes produce a host of inflammatory cytokines, and obesity is generally associated with a chronic state of inflammation in peripheral tissues[137]. Inflammation in brain sites that are involved in regulating food intake may play a key part in the development of obesity. In mice that are permitted to consume a high-fat diet and in overweight *ob/ob* mice, inhibitor of NF-κB kinase subunit-β (IKKB)–NF-κB signalling is abnormally elevated in neurons of the mediobasal hypothalamus (MBH)[138]. Moreover, genetic disruption of IKKB–NF-κB signalling in the MBH, and specifically in agouti-related peptide (AgRP) neurons in this site (FIG. 1), protects mice

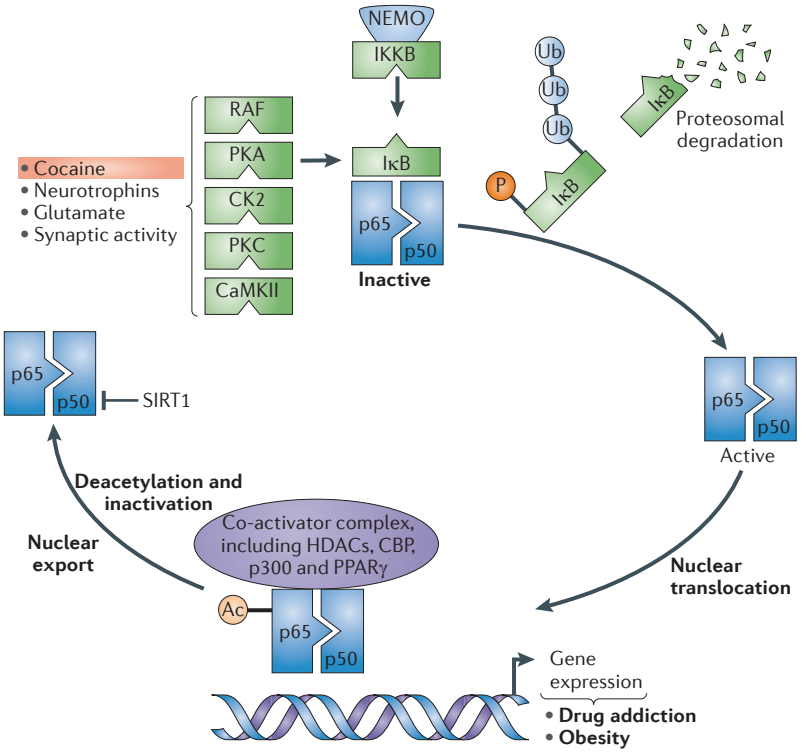

Figure 5 | **Nuclear factor-κB signalling and its regulation by SIRT1.** Immune, inflammatory and stress signals in the striatum converge on the inhibitor of Nuclear factor-κB (NF-κB) kinase subunit-β (IKKB). Neuronal activity that is triggered in response to cocaine, neurotrophins or glutamate transmission also activates IKKB. IKKB then phosphorylates IκB. IκB is the major inhibitory factor that retains NF-κB (usually a dimeric complex comprising the p65 and p50 subunits) in the cytoplasm and prevents its activation and translocation to the nucleus. Phosphorylation of IκB by IKKB leads to IκB ubiquitylation and proteolysis, rendering NF-κB free to translocate to the nucleus. IκB can also be phosphorylated by other kinases that are implicated in synaptic plasticity, drug addiction and feeding behaviour, including RAF proto-oncogene serine/threonine protein kinase (RAF1), protein kinase A (PKA), casein kinase 2 (CK2), protein kinase C (PKC) and calcium/calmodulin-dependent protein kinase type II (CaMKII). In the nucleus, activated NF-κB binds to response elements in the promoters of NF-κB-responsive genes such as histone deacetylases (HDACs), CREB-binding protein (CBP) and p300. Peroxisome proliferator-activated receptor-γ (PPARγ) has anti-inflammatory effects through an inhibitory action on NF-κB activity, probably by sequestering key transcriptional co-activators like p300 and CBP. Similarly, NAD-dependent deacetylase sirtuin 1 (SIRT1) has anti-inflammatory actions through its ability to deacetylate the p65 subunit of NF-κB and inhibit its activity. Ac, acetyl; NEMO, NF-κB essential modulator; Ub, ubiquitin.

from obesity when permitted to eat a high-fat diet[138], whereas ectopic activation of IKKB–NF-κB signalling in MBH triggers central insulin and leptin resistance (key physiological features of obesity)[138]. Brain-specific deletion of MYD88, an important adaptor protein through which toll-like receptors (core components of the innate immune system) activate NF-κB signalling, also protects mice from weight gain and developing leptin resistance when consuming a high-fat diet[139], further supporting a role for inflammatory signalling in the brain in obesity. In addition to overeating, enhanced NF-κB signalling in the hypothalamus, particularly within POMC neurons in the MBH, can trigger other obesity-associated disorders such as hypertension[140]. Obesity was also associated with inflammation in extrahypothalamic brain sites that are involved in hedonic aspects of feeding behaviour. Using MRI, obese human subjects were shown to have chronic inflammation of the OFC, an important brain site that is involved in the attribution of incentive value to palatable food (see above)[141]. Based on this finding, it was proposed that inflammation in cortical brain sites, and perhaps also in limbic, striatal and midbrain sites that are involved in regulating palatable food consumption, may contribute to the development of obesity.

Cocaine and other drugs of abuse can also trigger inflammatory responses in brain. In mice, cocaine activates NF-κB signalling in the NAc[142,143], leading to an increase in BDNF levels and enhanced sensitivity to cocaine reward[142]. Cocaine-induced NF-κB signalling also caused structural remodelling in the NAc, resulting in an increased number of dendritic spines on NAc neurons[142], which may be an adaptive response that increases vulnerability to addiction[142]. In addition to cocaine, consumption of alcohol also activates NF-κB signalling in brain, and it has been suggested that this contributes to the development of alcoholism[144].

SIRT1 in obesity and addiction. Given the importance of NF-κB signalling in weight gain and drug reward, it is perhaps not surprising that proteins that regulate NF-κB signalling — such as the NAD-dependent deacetylase sirtuin 1 (SIRT1) — are also implicated in obesity and drug addiction. SIRT1 has anti-inflammatory actions, primarily through deacetylating and inhibiting the p65 NF-κB subunit[145]. Genetic variation in the *SIRT1* gene is associated with lower BMI scores in humans[145], and genetic ablation of SIRT1 in hypothalamic POMC neurons increases the vulnerably of mice to diet-induced obesity by decreasing energy expenditure[146]. Cocaine increases expression of SIRT1 in the striatum[147] and resveratrol-induced activation of SIRT1 activity enhances the motivational properties of cocaine[147]. These findings suggest that SIRT1 in hypothalamus and striatum regulates food and drug intake, respectively. It will be interesting to determine whether these actions are related to NF-κB signalling, and whether SIRT1 activity in the striatum also regulates the hedonic properties of palatable food.

New vistas in obesity and addiction research

Tantalizing new observations are revealing glimpses of new systems and biological processes that may also be involved in obesity and addiction. For example, circadian rhythms may influence the sensitivity of brain reward circuitries and thereby regulate feeding behaviour and drug use. The transcription factors CLOCK and BMAL1 are core components of circadian master clock, which is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. CLOCK mutant mice are obese[148], are more sensitive to cocaine reward than wild-type mice and show enhanced excitability of midbrain dopamine neurons[149]. It will therefore be interesting to determine how CLOCK–BMAL-regulated genes influence food and drug intake.

RNA editing is a post-transcriptional process by which adenosine residues are edited to inosine in the sequence of mature mRNA transcripts, which

can result in alterations in the amino-acid code of the translated protein[150]. RNA editing is catalysed by double-stranded RNA-specific adenosine deaminases (ADARs), and perhaps the best-known mRNA transcript that is subjected to RNA editing in the brain is the serotonin 2C (5-HT_{2C}) receptor[151]. Disruption of ADAR2 activity in mice (ADAR2 is known to edit AMPA and kainate glutamate receptor subunits) results in hyperphagia and obesity in mice. Furthermore, the small nucleolar RNA HBII 52 controls editing of $5HT_{2C}$ receptors[152], and chromosomal microdeletions of HBII 85 contribute to the features of the neurodevelopmental disorder Prader–Willi syndrome[153], a major symptom of which is obesity. MicroRNAs are also involved in post-transcriptional regulation of gene expression and a key role for microRNAs in regulating the motivational properties of cocaine in rats and mice is emerging[154]. They have also been heavily implicated in adipogenesis, glucose metabolism and insulin signalling. However, very little is known of the role in feeding behaviour.

Agonists of peroxisome proliferator-activated receptor-γ (PPARγ), such as rosiglitazone (Avandia; GlaxoSmithKline plc), are used as insulin-sensitizing agents to treat type 2 diabetes. PPARγ also regulates adipogenesis and one of the major side-effects of PPARγ agonists is weight gain, particularly by targeting PPARγ that is expressed in brain[155,156]. PPARγ interacts with known regulators of drug intake, including NF-κB (FIG. 5), SIRT1 and CDK5, and PPARγ agonists decrease alcohol consumption and attenuate relapse-like behaviour[157]. Hence, it will be important to understand the precise mechanisms through which PPARγ and other nuclear hormone receptors regulate food and drug consumption, and to determine whether they act on the same signalling pathways.

Lastly, drugs of abuse decrease neurogenesis, the process by which new neurons are born and mature, in the brains of adult rodents[158]. Similarly, apoptosis of newly born neurons in the olfactory bulb, a process that may regulate odour-related memory, is increased in mice during the post-prandial period[159]. This suggests that neurogenesis in the olfactory bulb and perhaps other regions of the brain may contribute to aspects of feeding behaviour and drug use. Hence, it will be important to investigate the contributions of emerging mechanisms of neuroplasticity and gene regulation in the brain to the hedonic aspects of feeding behaviour and the rewarding properties of addictive drugs.

Summary

As discussed in this Review, many of the same brain systems regulate food intake and drug use, and similar adaptive responses can be triggered in brain reward systems by drugs of abuse and palatable food. As a result, obesity is now often conceptualized as a form of compulsive consummatory behaviour much like drug addiction. Thus, our understanding of the neurobiological mechanisms of drug addiction may provide a heuristic framework for deciphering the motivational drivers in obesity. Lastly, much emphasis is now being placed on defining the effects of palatable food on brain reward circuits that are implicated in drug addiction. However, it is also worth considering the reverse relationship that exists between the homeostatic feeding circuits in the hypothalamus and the brainstem in regulating consumption of addictive drugs. Nicotine and other drugs of abuse can stimulate hypothalamic feeding circuits and thereby influence weight gain[160]. It is an intriguing possibility that these hypothalamic feeding circuits may also regulate drug reward and contribute to the loss of control over drug use that characterizes addiction.

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FURTHER INFORMATION
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