Frontiers in Neuroendocrinology 31 (2010) 85–103

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

Appetite and reward

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ARTICLE INFO

Article history:
Available online 12 October 2009

Keywords:
Energy balance
Obesity
Reinforcement
Nucleus accumbens
Striatum
Lateral hypothalamus
Opioids
Endocannabinoids
Leptin
Insulin

ABSTRACT

The tendency to engage in or maintain feeding behaviour is potently influenced by the rewarding properties of food. Affective and goal-directed behavioural responses for food have been assessed in response to various physiological, pharmacological and genetic manipulations to provide much insight into the neural mechanisms regulating motivation for food. In addition, several lines of evidence tie the actions of metabolic signals, neuropeptides and neurotransmitters to the modulation of the reward-relevant circuitry including midbrain dopamine neurons and corticolimbic nuclei that encode emotional and cognitive aspects of feeding. Along these lines, this review pulls together research describing the peripheral and central signalling molecules that modulate the rewarding effects of food and the underlying neural pathways.

> "We recognize pleasure as the first good innate in us, and from pleasure we begin every act of choice and avoidance, and to pleasure we return again, using the feeling as the standard by which we judge every good." – Epicurus [Letter to Menoeceus, between 306 and 270 BCE] [87]

1. Introduction

In one of the first documented accounts of the role of pleasure in behaviour, Epicurus captures the notion of pleasure as the experience that profoundly shapes our evaluations, biases our actions and guides our future choices. The degree of pleasure that we experience when coming into contact with an object or when engaging in a particular behaviour can powerfully influence our approach or avoidance of that object or behaviour in the future. Consider how eating a delicious morsel of food propels you to take another bite. Pleasurable feelings play a significant role in behaviour.

Whether in conditions of hunger or satiety, food intake can be influenced by the pleasurable effects of food. Thus, the joy of eating can arise not only from the fulfillment of a vital physiological need but also from the sheer gratification derived from savoring appetizing foods. The word *pleasure* often refers to a complex experience that involves emotions such as happiness, enjoyment and satisfaction that are difficult to evaluate in the study of non-human animals. Alternatively, the term *reward* is commonly used in the scientific literature to refer to a more measurable quality of an object or action. As used here rewards (1) are objects or actions that prioritize behaviour and promote the continuation of ongoing actions, (2) increase the behaviours that lead to the procurement and/or consumption of the reward (positive reinforcement), and (3) direct future behavioural actions.

Subjective estimates of the reward value of food incorporate qualities such as taste, texture, smell and post-ingestive consequences, together with information about the amount and spatiotemporal distribution of food and the metabolic state of the organism [314]. Value representations along with information about the cues and properties associated with attaining food are stored in memory to guide future behaviours, such as orient animals back to the source of food. The heightened emotional and behavioural response to palatable high-fat and -sugar foods that

Abbreviations: Ach, acetylcholine; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; AMY, amygdala; ARC, arcuate nucleus; BSR, brain stimulation reward; CCK, cholecystokinin; DA, dopamine; DAT, dopamine transporter; DOR, delta opioid receptor; DS, dorsal striatum; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; HIP, hippocampus; KOR, kappa opioid receptor; LH, lateral hypothalamus; GP, globus pallidus; MFB, medial forebrain bundle; MOR, mu opioid receptor; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NT, Neurotensin; OFC, orbital frontal cortex; PBN, parabrachial nucleus; PVN, paraventricular nucleus; PI3, phosphatidylinositol-3; PYY, peptide YY; NTS, nucleus of the solitary tract; NMDA, N-methyl-D-aspartic acid; 5-HT, serotonin; SN, substantia nigra; STAT3, signal transducer and activator of transcription; TH, tyrosine hydroxylase; VP, ventral pallidum; VTA, ventral tegmental area.

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doi:10.1016/j.yfrne.2009.10.003

has evolved can be understood in terms of what these foods offer in caloric value. Indeed, the consumption of tasty, energy-dense foods can produce a rewarding effect that strengthens action–outcome associations and reinforces future behaviour directed at obtaining these foods. While the rewarding impact of eating high-fat and -sugar foods serves as an adaptive element in conditions of food scarcity the increased abundance and accessibility of these foods in many parts of the world has promoted excessive caloric intake and weight gain.

Identifying the neural circuitry and mechanisms responsible for the rewarding properties of food has significant implications for understanding energy balance and the development of obesity. Although this subject matter has received widespread attention in more recent years, there is an extensive and rich body of literature on the study of appetite and reward. By and large, these studies can be classified into two areas: Those investigating the impact of energy states, peptides and neurotransmitter systems on behavioural measures of the rewarding effects of food; and those examining the modulation of reward-relevant neural circuitry by manipulations of energy balance. To convey current understanding of the behavioural processes and neural mechanisms regulating food reward it is important to place it in the context of our knowledge and its evolution of the neural circuitry that underlies all rewards and motivated behaviours, especially since there is considerable overlap in the associated pathways. Along these general lines, this review discusses selected findings concerning: the neural basis of reward; the reward efficacy of food, and; the neural pathways and mechanisms linked to food reward.

2. Neural basis of reward

The rewarding effects of stimuli and behaviours have long been studied by measuring the willingness of the subject to work to gain access to the goal object. In the view of Thorndike, behavioural responses to stimuli that produce satisfying effects are likely to be repeated again [335]. The idea that response outcomes can direct subsequent behavioural actions was later formulized in Skinner's theory of reinforcement proposing that the consequence of a response acts as a positive reinforcer when the probability of that response occurring in the future is increased [318]. As a central tenet of *operant conditioning*, Skinner maintained that response strength can be determined by measuring the frequency or intensity of behavioural responses (e.g. lever presses) [318]. Operant (or instrumental) conditioning is a principle concept and procedure in the experimental analysis of behaviour and serves as an empirical construct in models of behavioural choice and reward measurement [17,159,187]. By measuring the willingness of the subject to work for the goal object, operant measures can offer a meaningful index of reward effectiveness.

The discovery by Olds and Milner in 1954 that rats will avidly work to self-administer electrical stimulation to some regions of the brain was a remarkable beginning to the study of brain reward circuitry [245]. In addition to the eruption in the scientific community provoked by this finding, newspaper headlines reading the "brain pleasure area" had been discovered and that "it may prove the key to human behaviour" stirred up much public excitement (The Montreal Star; March 12, 1954) [225]. Also known as brain stimulation reward (BSR), this phenomenon is considered to tap into the neural circuitry that conveys the rewarding properties of natural stimuli and behaviours. The rewarding stimulation generates a powerful grip on behaviour as revealed by the resistance to forgo delivery of the stimulation: Rats will cross electrified grids [244] and go without food in conditions of severe deprivation [73,289,325] in order to maintain contact with the manipulator that triggers the stimulation. Robust self-stimulation behaviour is obtained with electrodes along the medial forebrain bundle (MFB) and into the midbrain extension of the MFB [73,246]. Self-stimulation is observed from electrodes located in several brain areas, including the orbitofrontal cortex, nucleus accumbens (NAc), lateral hypothalamus (LH), ventral tegmental area (VTA) and brainstem structures. Studies combining electrophysiological linkage [284,315] and immunohistochemical mapping approaches [16,18] with BSR provide much insight into this multi-synaptic network of brain regions recognized for their contribution to reward-relevant processes, including those underlying motivation for food.

From the early findings that rats would continuously self-stimulate the LH while forgoing physiological needs, such as feeding and drinking, emerged the idea that the stimulation tapped into the neural circuitry sub serving natural rewards, such as food and water [243,289,325]. Consistent with this view, subsequent work showed that BSR establishes and maintains response patterns much like those generated by natural rewards [34]. Studies of BSR also provided some of the first suggestions that reward circuitry is subdivided along functional and anatomical lines. Rare observations of humans with self-stimulating electrodes revealed that stimulation at distinct loci could elicit different subjective reports [41]. Similarly, several lines of evidence obtained in rats provide strong support for anatomically segregated subpopulations of reward neurons that code for separate functions [42,62,112,114]. Investigations of the brain circuitry that gives rise to rewarding self-stimulation not only established a neural basis for reward but have made great strides in characterizing the properties of the directly activated neurons [363], their connections [312] and the manner in which reward circuitry is functionally organized [112,313].

The observations that manipulations of the brain dopamine (DA) system modulate BSR were among the first to implicate DA in reward-relevant processes. Certainly, the study of the neural basis of reward is well-rooted in investigations of DA circuitry. As the most studied and tied to reward-relevant functions are the mesocorticolimbic and nigrostriatal DA pathways that originate in the midbrain VTA and substantia nigra (SN), respectively, and project to various limbic and cortical sites including the NAc, amygdala (AMY), ventral pallidum (VP), dorsal striatum (DS), hippocampus (HIP) and prefrontal cortex (PFC). Early on it was shown that DA receptor antagonists [105] and lesioning of DA neurons via 6-hydroxydopamine (6-OHDA) [204] inhibit BSR whereas drugs that directly or indirectly increase DA tone, including amphetamine [115], cocaine [89], heroine/morphine [88,286] and nicotine [174] enhance the rewarding effects of MFB stimulation. Despite the potent impact on BSR produced by modulation of DA signalling, the traversing of DA fibers along portions of the MFB and the facilitatory action of MFB self-stimulation on DA release [139,256], the results of several studies suggest that the neurons directly activated by MFB stimulation are not dopaminergic [40,116,364]. However, the directly activated neurons may trans-synaptically activate DA neurons via a cholinergic input arising from the pedunculopontine or laterodorsal tegmental nucleus [266,365].

Much like the effects of electrical brain stimulation, central administration of drugs that modulate DA tone can be reinforcing (see [359]). Several lines of evidence suggest that the reinforcing actions of drugs of abuse are due, at least in part, to the modulation of DA signalling in the NAc. The actions of amphetamine [370], cocaine [172] and opiates [79] to increase instrumental responding are associated with enhanced DA release in the NAc. Rats will self-administer amphetamine directly into the NAc [166] whereas selective DA lesions in the NAc block self-administration of intravenous amphetamine [208]. Unlike amphetamine, rats will not learn to respond for cocaine administration into the NAc, but will self-administer cocaine into another DA terminal region, the

medial PFC (mPFC) [129]. Nonetheless, DA release in the NAc appears to be important in mediating the reinforcing actions of cocaine since DA lesions in the NAc impair intravenous cocaine self-administration [273]. Rats will also work for discrete injections of morphine and mu and delta opioid receptor agonists into both the VTA [347] and NAc [247], and injection of opiates into the VTA increases extracellular levels of DA in the NAc [79]. Although these data highlight the importance of NAc DA in drug self-administration, a role for the mPFC in the reinforcing effects of cocaine [130] and NMDA receptor antagonists (i.e., ketamine) [58] is well documented.

The results of experiments investigating the influence of DA on BSR and drug self-administration contributed to the popular notion that DA is responsible for rewarding behaviour. Changing dopaminergic tone influences the behavioural effectiveness of rewards such as BSR, drugs of abuse, food and sex, however there is disagreement concerning how and where DA neurons contribute to the circuitry underlying reward. Indeed, the exact functional contribution of DA has received intense attention on both the empirical and theoretical levels. Discrepancies in the DA literature are likely influenced by variations in DA terminal areas in the forebrain under investigation [80,321], differences in the electrochemical techniques used [274] and the behavioural measurements and models employed (see [23]).

Despite different views, a large body of work suggests that DA is important for reward-relevant learning and neural plasticity. This line of research emerged from the discovery that repeated administration of drugs that stimulate DA release can have long-lasting consequences by potentiating the behavioural effects of these drugs, a process known as sensitization. Recurrent drug administration has been shown to enhance locomotor-activating effects of psychostimulant drugs [188], drug self-administration [205,258], BSR [194] and opiate-induced feeding [237]. Notably, the behavioural sensitizing effects of repeated drug intake are linked to elevations in DA release [195] and long-lasting structural and molecular changes in DA neurons and their striatal targets [175,277,351]). Thus, substantial evidence has accumulated over the past two decades to support a role for DA in strengthening action–outcome associations; nonetheless, the precise contribution of DA in learning-related processes and neuroadaptations is still a matter of major investigation and discussion.

To summarize, investigations of BSR and drug self-administration have been instrumental for establishing the neural foundations of reward. Central to this research is the modulation of motivated behaviour by neurochemical manipulations revealing the contribution of neurotransmitter and peptide systems. Numerous findings that drugs that increase DA tone can be self-administered and that interfering with DA signalling in the mesolimbic pathway can dramatically alter BSR and drug self-administration emphasize the important role for DA in reward-relevant behaviour. Upon discussing the impact of DA in feeding in later sections, I will touch on work characterizing the impact of DA on different motivational and neural processes. This research deserves particular attention to gain a thorough understanding of the contribution of DA to feeding behaviour and motivation for food. As this literature will not be systematically reviewed here, the reader is referred to the following reviews [38,138,257,268,294,302].

3. Reward efficacy of food

Behaviour is an essential component of the energy balance equation. Appetitive and consummatory behaviours are the sole means through which energy intake is achieved, and all behaviour entails energy expenditure. The rewarding properties of food can dramatically influence the propensity to engage in or continue feeding behaviour. The reinforcing effects of food have commonly been assessed using operant conditioning procedures that measure the willingness to work for food. In other instances, food reinforcement has been studied using the conditioned place preference model. The conditioned place preference paradigm entails Pavlovian (associative) conditioning in which the reinforcing effects of the object are evaluated by measuring the amount of time the animal spends in an environment previously paired (associated) with that object [344]. Therefore, both operant conditioning and conditioned place preference models measure acquired and voluntary behavioural responses that are directed at obtaining the goal object and influenced by prior encounters with the goal object (“goal-directed behaviour”).

The *hedonic* properties of food are commonly assessed by determining the affective evaluations that are generated in response to direct encounters with food or food-related stimuli. In the case of human participants, the respondent provides a subjective evaluation of a sensory property of food (often taste) which is reflected by a rating of pleasantness or liking. The hedonic attributes of food have also been studied in animals using the taste reactivity paradigm which measures spontaneous oral and facial reaction patterns to tastants that are inherent across many mammalian species [37]. Research employing these hedonic measures of food reward will be reviewed here, however relevant work addressing the role of taste, macronutrient preferences and palatability will not be thoroughly covered. Therefore, the reader is referred to excellent reviews on taste [222,317], food preferences [290,304,305] and palatability [53,220].

A commonly used measure of the reward efficacy of food is an operant procedure known as the progressive ratio (PR) schedule of reinforcement. In the PR task, the subject is required to emit an increasing number of operant responses for each successive reward. Eventually performance falls below a preset criterion. The number of responses emitted to obtain the last reward (“break point”) serves as an index of the willingness to work [162]. While operant procedures that measure changes in response rate alone cannot dissociate changes in reward efficacy from alterations in performance capacity (e.g., [196,223]), the break point derived from the PR schedule is a well-validated measure of the reward magnitude of food [162,163].

3.1. Energy states and metabolic signals

Initial reports of PR performance for food in rats demonstrated that the break point declines when the caloric value of the food is reduced whereas it increases as a function of weight loss and the quantity of food [162,163]. Both food restriction [162,269] and acute food deprivation [183] increase break points and thus enhance the rewarding effects of food. Break points on the PR schedule are positively correlated with sucrose concentration demonstrating that motivation for sucrose increases in a manner that follows sweet taste [47]. Furthermore, food restriction and weight loss are reported to increase sucrose motivation as a function of the concentration of sucrose [269]. These findings are comparable to those obtained in human participants that rated sucrose solutions as more pleasant following a period of food restriction and weight loss [55]. Interestingly, while the reward efficacy of food is elevated during conditions of energy deficit [162,183,269] it is also elevated in states of increased adiposity. PR performance for chow or sucrose is enhanced in obese Zucker rats relative to lean controls [127,267] in diet-induced obese rats [200], obesity-prone rats following discontinuation of a high-fat and – sugar diet [260] and in overweight as compared to lean children [333]. These findings illustrate how PR measures can track changes in the quality of a food reward and the energy needs and motivational state of the organism.

Human studies were the first to describe the impact of metabolic manipulations on hedonic evaluation of food. Thompson and Campbell found cellular glucopenia induced by peripheral 2-deoxyglucose (2-DG) administration increased ratings of the pleasantness of a sucrose solution [334]. Similarly, systemic administration of insulin was reported to enhance sucrose pleasantness ratings [48,49]. The process whereby insulin increases affective ratings may be attributable to reductions in central glucose signalling elicited by insulin given that sucrose ratings correlated negatively with blood glucose concentrations. However, Jewett and colleagues found that glucoprivation induced by peripheral 2-DG in rats failed to alter break points in a PR task for food while it increased the amount of freely available food consumed. The distinction between the above findings may not be simply due to species differences but rather the different measurements used, thus 2-DG may enhance affective ratings for sweet taste without modulating willingness to work measures for sucrose. Such a discrepancy between affective and instrumental measures has been described and likely reflects the different neural mechanisms recruited [36].

Evidence obtained in rats suggests that insulin has specific actions in the CNS to modulate the reward efficacy of food. Intraventricular (ICV) administration of insulin not only decreases free-feeding intake [361] but can inhibit PR responding for sucrose [98]. Moreover, Figlewicz et al. report that the effects of insulin to decrease responding for sucrose is mediated via signalling in the arcuate nucleus (ARC) [97]. These investigators also find that the adipose-derived hormone leptin can attenuate sucrose-reinforced responding. The above result stands in contrast to findings that ICV administration of insulin fails to alter breakpoints in a PR task for food [183]. The discrepancy between the two studies could be due to the response measures used given that the rates of responding for sucrose recorded by Figlewicz et al. may be more sensitize than the breakpoint index measured by Jewett et al. Figlewicz et al. also report that insulin and leptin decrease conditioned place preference for high-fat food and thereby provide additional evidence that circulating satiety hormones reflecting the status of long-term energy stores can suppress the reinforcing actions of palatable foods [96].

Apart from insulin and leptin, several other circulating peptides act centrally to decrease food intake. Cholecystokinin (CCK) is a gut-derived satiety signal that has been linked to reward-relevant neural processes [346]. Systemic CCK injection diminishes the ability of food deprivation to increase instrumental responding for food suggesting that peripherally-derived CCK can modulate the reinforcing effects of food [25] . Furthermore, CCK-1 receptor deficient rats (OLETF) that are hyperphagic and obese exhibit enhanced instrumental responding for sucrose relative to wildtype controls [146]. Released from intestinal cells in proportion to caloric intake, peptide YY (PYY) is another gut peptide implicated in appetite control [30,31]. In an instrumental task, peripheral administration of PYY-36 failed to inhibit responding for high-fat food pellets, however it reduced reinstatement of food-seeking induced by exposure to the high-fat food and a cue associated with the food [125]. Together, these data demonstrate the effects of some peripherally-derived satiety signals to suppress the rewarding effects of food. There are a number of circulating peptides that have yet to be studied in the context of food reinforcement. Specifically, it is not known whether other signals release from the digestive tract, including ghrelin, glucagon-like peptide 1 and enterostatin, can modulate the reward efficacy of food. As will be reviewed later however, there is evidence tying the actions of ghrelin along with leptin, insulin and PYY to the modulation of reward circuitry.

3.2. Endocrine neuropeptides

There has been remarkable progress in the identification and characterization of the hypothalamic and hindbrain neuropeptides that respond to hormonal and metabolic signals from the periphery to influence energy balance (this issue). Several neuropeptides localized in the ARC are known to regulate food intake, including the orexigenic signals neuropeptide Y (NPY), agouti-related peptide (AgRP) and anorexigenic signals alpha-melanocyte-stimulating hormone (αMSH) and cocaine and amphetamine-regulated transcript (CART). In addition to stimulating free-feeding intake, central administration of NPY potently increases the reward efficacy of chow [183] and sucrose [52] by increasing breakpoints in a PR schedule of reinforcement. NPY is also synthesized in neurons outside of the hypothalamus which have been linked to reward-relevant processes [186], however the actions of NPY to increase motivation for food appears to be mediated by hypothalamic NPY as direct administration of NPY into the perifornical LH increases PR performance for sucrose [52]. Coexpressed with NPY, AgRP also elicits a profound increase in food intake. The actions of AgRP to selectively increase fat appetite appears to be mediated via the MC4 receptor [296] and mice lacking the MC4 receptor develop increased motivation for food in a PR task relative to wildtype littermates [348]. Moreover, recent evidence demonstrates that AgRP administration in rats can selectively increase the reward efficacy of high-fat food, but not sucrose, in a PR task [341]. These results provide evidence that the motivational properties of food can be divided along nutritional lines.

There is less evidence linking anorexigenic neuropeptides to the rewarding effects of food. Several lines of evidence link CART to mechanisms mediating the reinforcing actions of psychostimulant drugs [171,280], yet while CART administration into the NAc decreases breakpoints for cocaine reward it fails to alter motivation for food [179]. Similarly, corticotropin-releasing hormone (CRH) decreases food intake in rats [50,134], however CRH has been reported to increase [233], decrease [8] or fail to alter [250] response rates and the number of food reinforcers earned. In other studies, central administration of a CRH-1 and/or CRH-2 receptor antagonists did not influence instrumental responding for food [128]but a CRH-1 antagonist can attenuate the effects of stress-induced reinstatement of lever-pressing for palatable food [124]. Modulation of the CRH system does not appear to suppress the reward efficacy of food, rather the actions of CRH to reduce food-motivated responding appear to be limited to impairments in motor capacity [7]. Neurotensin (NT), on the other hand, is among the anorexigenic signals consistently reported to inhibit instrumental responding for food. NT injections into both the lateral ventricles [288] and VTA [190] decrease operant responding for food whereas peripheral administration of a NT analog inhibits sucrose-reinforced responding [45]. While NT is expressed in the hypothalamus there also exist NT neuronal populations outside of the hypothalamus with ties to feeding and reward [120].

Orexin-A and orexin-B are synthesized exclusively in a subset of LH neurons innervated by the ARC neuronal populations described above. Numerous reports over recent years demonstrate the impact of orexins on reward circuitry and its influence on goal-directed behaviour. Orexin-A infusion into the rostral LH elicits a particularly robust feeding response [338] and enhances breakpoint responding for sucrose pellets [337]. In contrast, systemic infusion of an orexin-1 receptor antagonist failed to alter instrumental responding for sucrose [270]. However, in another study peripheral administration of an orexin-1 receptor blocker attenuated instrumental responding for high-fat food pellets [234]. Orexin neurons project to the VTA [90] and orexin-A and orexin-B potentiate excitatory inputs to VTA DA neurons by mechanisms involving both orexin-1 and -2 receptors [43,44]. In addition, Borgland et al. report that orexin-1 receptor antagonism blocks cocaine-induced locomotor sensitization and potentiation of excitatory currents in VTA DA neurons [44]. These and other findings implicate orexins in DA signalling and synaptic plasticity and in

the modulation of goal-directed behaviour for food. Like orexin, melanin-concentrating hormone (MCH) is produced exclusively in the LH, however in a discrete neuronal subpopulation [84]. Matching the pattern of MCH axonal projections, the MCH-1 receptor is expressed in numerous brain regions including the NAc and DS [293]. Georgescu et al. reveal a specific role for MCH signalling in the NAc shell by demonstrating the effects on an MCH-1 receptor antagonist to inhibit feeding and produce anti-depressant like effects [121]. Consistent with these results, work of Pissios et al. demonstrates enhanced behavioural responses to amphetamine and increase stimulation-evoked DA release in the NAc shell of MCH deficient mice [261]. Despite these data, it remains to be elucidated whether or not MCH enhances the reinforcing effects of food.

In summary, the data reviewed in this section illustrate that several neuropeptides controlling appetite and energy balance, including NPY, AgRP, NT and orexin, can modulate goal-directed behaviour for food. It is interesting that studies employing nuclei-specific microinfusions suggest that the effects of insulin, NPY and orexin on PR performance for food are obtained with targeted injections into hypothalamic regions. This is not surprising in consideration of the multiple reciprocal connections between hypothalamic nuclei and reward-relevant substrates. As discussed later, leptin, insulin and ghrelin also regulate DA tone by targeting midbrain DA neurons to suggest there are at least some direct actions of these hormones on reward-relevant processes.

3.3. Opioids

The neuropeptide group most investigated in the context of the rewarding effects of food and palatability are opioids, namely enkaphalins, dynorphins and endorphins. Each of these opioids can influence feeding behaviour by acting on opioid receptors (mu, kappa and delta) located throughout the brain. Non-selective opioid receptor blockade by peripheral [279,299] and central [176] naloxone administration decreases food intake in rats, especially when highly preferred foods such as sucrose or saccharin are used [14,126,207]. The effect of central opioid action to modulate feeding appears to be due, in part, to actions in the NAc and VTA. Direct administration of opioid agonists into the NAc stimulates food intake [212,230] whereas VTA administration of opioid agonists [230] or antagonists [309] increases and decreases food intake, respectively. The influence of opioids in the VTA and striatum to stimulate appetite are mainly attributed to mu opioid receptors (MOR) [21,239,373]. The important role of MOR-induced feeding in the striatum is underscored by the work of Kelley and coworkers. Stimulation of MOR and delta (DOR), but not kappa (KOR) receptors in the dorsal and ventral striatum increases intake of chow and sucrose, while particularly robust increases in food intake are seen following infusions into the NAc shell [21,373]. These investigators further show that MOR stimulation in the NAc shell by D-Ala^2, N-MePhe^4, Gly-ol-enkephalin (DAMGO) preferentially and dramatically increases intake of high-fat food [372,374]. Increased intake of palatable foods by NAc DAMGO injection is mediated by the LH given that GABA receptor blockade in the LH blocks the feeding response [356]. Characterizing the neural outputs mediating NAc MOR-induced feeding, Zheng et al. demonstrated that orexin neurons of the LH and their projections to the VTA are involved [375]. Apart from striatal regions, DAMGO administration in the VP [320] is also reported to increase food intake. Together, these data illustrate the unique role of MOR signalling in the VTA, NAc shell, DS and VP in the modulation of palatability and feeding by opioids.

Several lines of evidence support the idea that opioids influence both affective evaluations and goal-directed behaviour for food. In humans, systemic administration of non-selective opioid receptor antagonists suppress preference for sucrose [92] and decrease pleasantness ratings for the smell and taste of food [367]. Moreover, naltrexone administration is reported to be more effective at reducing pleasantness ratings for highly palatable foods, regardless of macronutrient content [366]. Consistent with these data, morphine enhances affective responses of rats for palatable foods as measured by the taste reactivity test [82]. Characterizing the receptors and brain sites mediating these opioid-induced responses, Berridge and coworker found that morphine infusion in the NAc shell [253] and DAMGO in the VP but not the LH [320] enhances taste reactivity patterns to sucrose.

The use of instrumental response measures demonstrate that opioids can alter goal-directed behaviour for food. Peripheral injection of the non-selective opioid agonists, buprenorphine [210] and morphine [322], increased break points for food on a PR schedule of reinforcement whereas administration of naloxone produced the opposite effect [26,68,153,291]. A role for MOR signalling in the NAc in the modulation of goal-directed behaviour for food is suggested by the demonstration that NAc DAMGO increases breakpoint responding for sugar pellets [371]. MORs have a high affinity for enkaphalins and endorphins and a low affinity for dynorphins (which are selective for kappa receptors), and both enkaphalin and beta-endorphin are released in the NAc and VP. Consistent with the above results, a series of studies by Hayward, Low and colleagues suggest that enkaphalin and beta-endorphin are the endogenous opioid receptor ligands that mediate the actions of opioids on the motivational properties of food. With the use of genetically engineered mice lacking enkaphalin and beta-endorphin these investigators report impaired breakpoint responding for food in a PR task in knockouts relative to wildtype controls [154–156]. Collectively, these findings highlight the important role of the MORs and ligands, enkaphalin and beta-endorphin, in the NAc and VP in the rewarding effects of food and the modulation of food palatability.

3.4. Neurotransmitters

As with BSR and drugs of abuse, the reinforcement efficacy of food can be modulated by alterations in DA tone. Systemic injections of a D1/D2 receptor antagonist can decrease instrumental responses [2,26] and conditioned place preference for food [326] yet fails to alter taste reactivity measures [342]. Similarly, a D2/D3 receptor antagonist decreases PR performance for sucrose pellets [67] without affecting taste reactivity patterns [254]. The D2 but not the D3 receptor appears to be specifically involved in food-reinforced responding given that a selective D3 receptor agonist fails to modulate PR performance and conditioned place preference for food [83]. Consistent with these findings, specific ablation of DA neurons in the NAc using 6-hydroxydopamine (6-OHDA) significantly attenuates goal-directed behaviour for food [2,149], but does not influence taste reactivity measures in rats [39] and either fails to alter or slightly augments free-feeding intake [196,295]. In an opposite manner, Zhang et al. discovered that increasing DA signalling in the NAc shell (and to a lesser extent the NAc core (but see [27]) via direct amphetamine administration increases the willingness to work for sugar pellets on a PR schedule of reinforcement [371] whereas others found that it actually inhibits free-feeding intake [191,192] and fails to alter taste reactivity patterns [362]. The influence of DA on goal-directed behaviour for food is not limited to the NAc as viral restoration of DA to the DS in DA-deficient mice rescues learning and performance of an instrumental task for food [275].

During encounters with food animals rapidly learn about the sensory qualities and the environmental cues associated with attaining food. These representations are stored in memory to help guide subsequent behavioural actions directed towards feeding.

The findings above illustrate how different measures provide a useful way to disambiguate the influence of DA in distinct facets of motivation for food. Collectively, the data suggest DA is important for learning about and maintaining goal-directed behaviour for food rather than food consumption by itself or processes, such as affective reactions, that are closely connected with the consummatory phase of feeding. This view bodes well with several investigations of Salamone et al. demonstrating the impact of DA manipulations on the effort required in work-related instrumental response measures [294]. There is also general agreement in the associative learning literature that DA is important to acquire information about rewards and the behavioural responses to obtain them. Peripheral administration of DA receptor antagonists inhibits the development of conditioned place preferences for palatable foods without affecting food consumption [6,178]. In addition, D1 receptor blockade in the LH [64] and NAc shell [95] can prevent learning of a taste aversion whereas D1 receptor blockade in the NAc core [319] and medial PFC [24] impairs learning of an instrumental task. Finally, systemic D1 receptor blockade [20] or specific D1 blockade in the NAc shell or core [340] attenuates acquisition of flavor preferences conditioned by intragastric glucose. Intriguingly, the results derived from studies of DA-deficient mice suggest that some form of learning or memory formation can still take place in the absence of DA, but is only evident in the context of goal-directed behaviours when DA is restored to the DS [276].

By signalling at nicotinic and muscarinic receptors, central cholinergic systems also participate in the regulation of appetite. As the major addictive component of tobacco, nicotine acts centrally to reduce food intake whereas smoking cessation is accompanied by hyperphagia and weight gain [143]. Nicotine administration into the LH suppresses food intake [228], an effect mediated by activation of nicotinic receptors located on GABA terminals that results in the inhibition of local MCH neurons [184]. On the other hand, muscarinic receptor blockade in the SN [358], NAc or DS [262,264] or selective lesion of acetylcholine (Ach) neurons in the NAc [147] potently decreases food intake. The action of muscarinic receptor antagonists in the striatum to decrease food intake is associated with reductions in enkaphalin gene expression, and thus reduced enkaphalin binding to MORs may mediate the anorexigenic effects [264]. Non-selective muscarinic, but not nicotinic, receptor blockade in the NAc core or shell suppresses breakpoints in a PR task for sucrose and inhibits learning an instrumental task [263]. Similarly, selective Ach lesion in the striatum impairs reward-related learning [193]. However, other investigators find that microinfusions of a muscarinic agonist in the NAc does not increase responding for food in a PR task [216]. Despite discrepancies in the above findings, several studies implicate striatal Ach activity and release in satiety-related responses [157,165] and encoding of rewarding and aversive outcomes [15,185]. These actions of striatal Ach are attributed to a small population of cholinergic interneurons that target muscarinic and nicotinic receptors expressed on local striatal neurons and axonal inputs from midbrain (including DA neurons) and corticolimbic regions [376].

A common pharmaceutical target for weight loss treatment, serotonin (5-HT) has long been known to influence appetite. By means of pharmacological and genetic tools, 5-HT1B, 5-HT2C and 5-HT6 subtypes were shown to be the primary receptors through which 5-HT exerts its anorectic effects [201]. Chronic blockade or deletion of the 5-HT transporter decreases instrumental responding for food [298]. Direct infusion of 5-HT into the NAc inhibits operant responding for food in a PR task, an effect that is not mediated by the 5-HT1B receptor [103]. However, peripheral infusion of a selective 5-HT2C agonist is reported to decrease PR responding for food suggesting a role for this receptor in mediating the action of 5-HT on the reward efficacy of food [142]. Interestingly, 5-HT2C receptors are located in the NAc and VTA among other loci, and 5-HT release in the VTA from axons originating in the dorsal raphe inhibits DA release [10]. These findings illustrate the impact of 5-HT to attenuate instrumental responding for food, an effect that may be mediated by the actions of 5-HT to reduce DA neurotransmission.

Serving as the primary inhibitory and excitatory amino acids in the brain, gamma-aminobutyric acid (GABA) and glutamate elicit disparate effects on feeding depending on the site of injection and feeding measurement employed. A GABA(A) receptor agonist in the NAc shell potently increases food intake yet does not augment PR responding for food [371]. Correspondingly, increasing GABAergic tone via peripheral delivery of a GABA transaminase inhibitor [199] or the GABA(B) agonist, baclofen, either modestly decreases instrumental PR responding for food or has no effect [46,202,251,272]. Nevertheless, in one other case systemic infusion of baclofen significantly reduced responding for a fatty food more so than normal chow [360]. Like GABA, glutamate signalling in the NAc shell modulates food intake, an effect mediated via actions at AMPA and kainate receptors [213,329]. Operant responding for food is reduced following peripheral AMPA antagonist (NBQX) administration, but this result appears to be due to impairments in motor function [327]. In addition, blocking metabotropic glutamate receptor 5 (mGluR5) by peripheral MPEP infusion did not alter food-maintained responding in two reports [118,218] yet reduced breakpoints for food in one other study [252]. While both GABA and glutamate plays a critical modulatory role in neurotransmission in brain regions implicated in the rewarding effects of food, the data taken together do not provide strong evidence that these neurotransmitters by themselves have an important influence on food-reinforced responding.

Collectively, the results of behavioural studies cited above implicate DA, Ach and 5-HT neurotransmitter systems in the modulation of food reward. Targeted modulation of DA and Ach tone in limbic areas brings to light the influence of D1, D2 and muscarinic receptor signalling in the NAc and dorsal striatum in the acquisition and strength of food-motivated instrumental behaviour. Similarly, one can speculate that the effects of 5HT2C receptor stimulation to inhibit food-motivated responding could involve receptors expressed in the NAc. It is interesting that while these neurotransmitter systems are implicated in the voluntary and learned behavioural responses for food they do not appear germane to affective taste reactions. Research is shedding light on the possible configuration of these pathways for the regulation of food reward. Immunohistochemical localization of the various receptors reveals that the interaction between Ach, DA and opioid systems in the NAc is complex (see Fig. 2). Clearly, more work is needed in order to tease apart the neural pathways and signalling events that are involved.

3.5. Endocannabinoids

The endocannabinoids, 2-arachidonoylglycerol (2-AG) and anandamide, are lipid molecules that bind to cannabinoid (CB) receptors to engage in numerous biological functions [81]. Located on presynaptic terminals releasing GABA or glutamate, the CB_1 receptor is widely expressed in the brain, including moderate to strong levels of expression in cortex, HIP, AMY, striatum and HYP. Due to its localization on inhibitory and excitatory presynaptic terminals, retrograde activation of CB_1 receptors can regulate the release and/or signalling of several neurotransmitters and neuropeptides, including dopamine, MCH and orexin and are thus considered neuromodulators.

The endocannabinoid system has received much recent attention for its role in regulating food intake and palatability. As the ac-

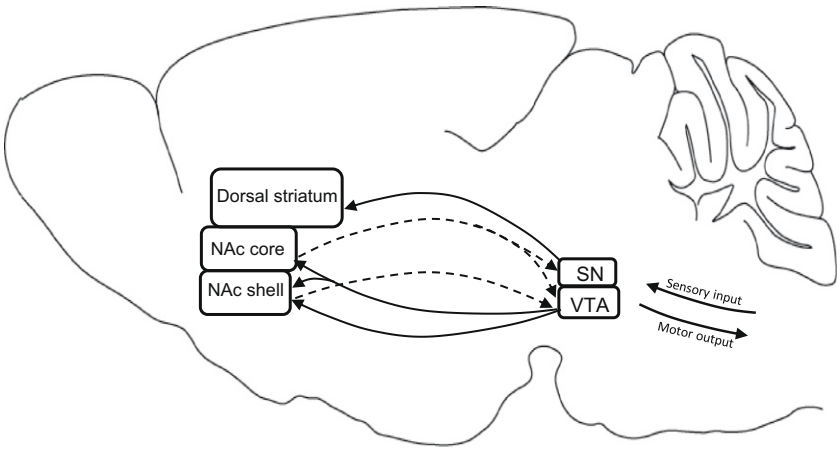

Fig. 1. Model of basal ganglia circuit organization [11,145]. This prominent model consists of parallel ascending cortico-basal ganglia–thalamus–cortico "loops". The NAc sends projections back to the source of DA neurons in the midbrain VTA. VTA DA neurons that receive afferents from the NAc shell send DA projections back to the NAc shell and core. In turn, NAc core neurons project back to the DA neurons from which they received input in addition to DA neurons of the SN that innervate the DS [145,177]. This model has been used to explain the process whereby goal-directed behaviour persists and can eventually develop into a habit by a gradual shift in its control from ventral striatal regions to more dorsal areas of the striatum [33].

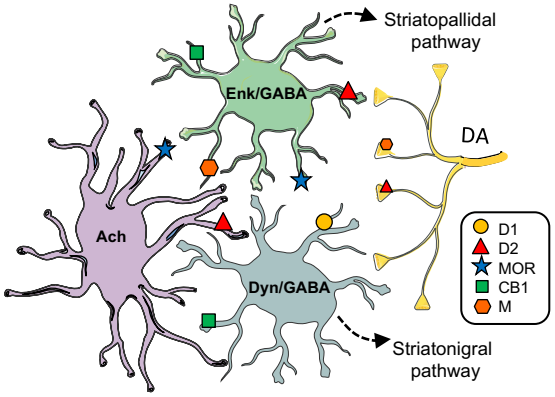

Fig. 2. Striatal targets of midbrain DA neurons and their outputs. GABAergic medium spiny neurons exist in two subpopulations: (1) GABA/dynorphin neurons that mainly express D1 receptors and project directly to basal ganglia output nuclei including the SN (striatonigral pathway), (2) GABA/enkaphalin neurons that express high levels of D2 receptors and MORs and project indirectly to basal ganglia output nuclei (striatopallidal pathway). Only the signalling molecules and receptors (denoted by symbols) implicated in the rewarding effects of food are illustrated. Ach, acetylcholine; CB1, cannabinoid-1 receptor; D1; dopamine-1 receptor; D2, dopamine-2 receptor; Dyn, dynorphin; Enk, enkaphalin; M, muscarinic receptor (mostly M1 and M4); MOR, mu opioid receptor. Illustration created thanks to *Servier Medical Art*.

tive ingredient in cannabis, delta-9 tetrahydrocannabinol (THC), has long been known to increase food intake, particularly for palatable sucrose [1,161]. Moreover, THC enhances the rewarding effect of food by increasing PR responding for food pellets [160,322]. A specific role for the CB_1 receptor in the reinforcing actions of food is highlighted by several demonstrations that CB_1 antagonism decreases instrumental responding for foods [209,267,336,354]. These data are supported by finding obtained in CB_1 receptor knockout mice demonstrating reduced responding for sucrose [297]. However, when standard food pellets served as the reinforcer, CB_1 receptor knockout mice were not different than controls [324]. Indeed, the effects of a CB_1 receptor antagonist or agonist to decrease and increase, respectively, food-reinforced responding are reported to be selective for a sweet reinforcer as compared to a pure fat reinforcer [354].

Much like opioid-induced feeding, a particularly robust stimulatory effect of the endogenous CB_1 receptor ligand, anandamide, can be obtained with targeted injections in the NAc shell region [211]. Moreover, anandamide injections in the NAc shell significantly increase affective taste reactivity patterns for a sucrose solution [211]. There is growing evidence for an interaction between endocannabinoids and opioids in the regulation of food preferences and food reward. Solinas and Goldberg discovered that the effect of THC to increase breakpoints for food in a PR task could be blocked by the non-specific opioid antagonist naloxone [322]. In turn, these authors show that the effect of morphine to enhance breakpoints is prevented by administration of the CB_1 antagonist rimonabant. Intriguingly, CB_1 receptors are co-localized with MORs on the processes of striatal medium spiny neurons [259] and there is evidence for functional interaction between these receptors in the NAc that regulates the release of GABA and glutamate [301]. To summarize, endocannabinoids in the NAc shell enhance the rewarding effects of food, possibly via a CB_1 receptor – MOR interaction. CB_1 receptors are also present in the VTA where they increase DA firing and release [66], and thus endocannabinoid action in the VTA may contribute to the modulation of food reward.

3.6. Conclusion

A great deal has been discovered about the signals and neural pathways contributing to the rewarding effects of food by investigations of the neurochemical and genetic basis of affective and goal-directed behaviour for food. The NAc shell stands out as a key brain region that coordinates neurotransmitter, opioid and endocannabinoids signals to control feeding behaviour. Among the important signalling molecules in the NAc shell are DA, Ach, opioids (enkaphalin and beta-endorphin) and cannabinoids and their respective actions at DA (D1 and D2), muscarinic (likely M1 and M4), MOR and CB1 receptors. The means by which these different signals interact to differentially modulate free-feeding intake, food-motivated behaviour versus affective reactions for food remains to be fully elucidated. For instance, MOR and CB_1 receptor activation in the NAc shell enhances goal-directed and affective responses for palatable foods in addition to free-feeding intake. In contrast, increasing DA signalling in the NAc strengthens instrumental behaviour yet fails to augment free-feeding intake and taste reactivity responses. Finally, while GABA A receptor activation in the NAc shell stimulates free-feeding it fails to augment PR responding for food. The distinction between the behavioural responses produced by these signals undoubtedly lies in the spe-

cific neuronal subpopulations and outputs involved. Research has made progress in delineating the anatomical and physiological interactions between neurotransmitter and peptide systems in midbrain and corticolimbic areas. The findings from these studies, which will be elaborated on in the next section, can provide valuable input for dissecting the processes underlying different facets of food reward. As this circuitry is uncovered we will be able to gain more insight into the genes and epigenetic modifications that promote individual susceptibility to intake of rewarding high-fat and sugar foods as a means to determine which mechanisms are contributing to overeating and obesity.

4. Neural pathways and mechanisms of food reward

4.1. Corticolimbic circuitry: basic anatomy and function

The central nervous system integrates numerous metabolic signals from the periphery and thereby generates adaptive behavioural responses to changing energy demands. Information about the metabolic state of the organism is preferentially encoded in hypothalamic and hindbrain sites whereas emotional and cognitive aspects are processed in limbic and cortical loci that assign salience and motivational valence to objects and behavioural actions. As used here, corticolimbic substrates refer to components of cortex, striatum and pallidum which each give rise to descending projections to the motor system (including *basal ganglia* output nuclei) whereby motivation is converted into action [331]. This circuitry is organized such that ventral components, including the AMY and NAc, are more implicated in the processing of emotions and emotional learning, and more dorsal portions, including the PFC and DS, are more involved in cognitive processes and habit formation [11,12].

The neural networks that give rise to goal-directed behaviour rely on basal ganglia outputs to channel motivation into behavioural action. Central to many research and theoretical approaches is an influential model of basal ganglia circuit organization which consists of parallel ascending cortico-basal ganglia–thalamus–cortico "loops" (Fig. 1) [11,145]. As a component of one circuit, the NAc sends projections back to the source of DA neurons in the midbrain VTA. VTA DA neurons that receive afferents from the NAc shell send DA projections back to the NAc shell and core. In turn, NAc core neurons project back to the DA neurons from which they received input in addition to DA neurons of the SN that innervate the DS [145,177]. Although often linked with regulation of motor control, the DS and its DA inputs from the SN are well-implicated in reward-relevant learning and habit formation [33,94,249]). This model serves as an intriguing conceptual framework to describe the process whereby goal-directed behaviour becomes less flexible and more persistent (as during the development of addiction) by a gradual shift in its control from ventral striatal regions to more dorsal areas of the striatum [33]. While the relevancy of this model to the behavioural controls of feeding remain to be empirically tested, it is interesting to consider how such processes may participate in motivation and craving for palatable high-energy foods and overeating.

The striatum receives the bulk of DA afferents from the midbrain. The majority of striatal neurons are medium spiny neurons that are so-called because of their high spine density (Fig. 2). There is also a small subset of cholinergic interneurons localized to the striatum with dense local arborizations [140,376] that are implicated in satiety-related mechanisms [157,217], sucrose bingeing [19] and in the encoding of rewarding and aversive outcomes [185]. Medium spiny neurons express GABA and can be grouped into at least two different subtypes based on their axonal projections and gene expression [122,123]. As illustrated in Fig. 2, one subpopulation consists of GABA/dynorphin neurons that mainly express D1 receptors and project directly to basal ganglia output nuclei including the SN, also known as the direct or striatonigral pathway. The other pathway consists of GABA/enkaphalin neurons that express high levels of D2 receptors and MORs and project indirectly to basal ganglia output nuclei via the external GP and subthalamic nucleus, also known as the indirect or striatopallidal pathway. Integration between these parallel striatal outputs and their corresponding circuit loops (as described above) is considered to be essential for coherent behaviour [132], and Ach interneurons are purported to play a role in the communication between the different pathways and striatal compartments [141,227]. Each striatal output pathway is differentially modulated by DA: DA excites the direct pathway via the D1 receptor whereas it inhibits the indirect pathway by way of the D2 receptor [330]. In this regards, it is interesting that the majority of NAc neurons differentially respond to either primary rewarding or aversive taste stimuli and to the cues that predict of their availability. Specifically, some NAc neurons are inhibited by tasting a sucrose solution (or exposure to a cue paired with sucrose) whereas others are excited by an aversive quinine solution [281,283], and these actions are opposite to the effects of these tastants on DA neurotransmission in the NAc shell [283]. While these findings demonstrate anatomically and functionally distinct NAc outputs in response to rewarding versus aversive taste stimuli it should be noted that it is not known whether these differences reflect direct and indirect striatal output pathways.

The NAc is considered as an interface for emotion, motivation and action due to its excitatory glutamatergic inputs from limbic and cortical structures such as the AMY, HIP and PFC [229,369]. Among the limbic inputs to the NAc is the AMY which receives food-related sensory information from the hindbrain and the cortex, in addition to physiological signals related to hunger and satiety via hindbrain nuclei [242]. Moreover, the AMY is a key substrate for processing emotion [113] and associative conditioning of food-related instrumental responses [169]. These and other observations suggest that the AMY connects external and internal sensory information with motivational systems of the brain. Providing additional input to NAc, the HIP serves a crucial role in memory formation and retrieval of internal and external cues, and new developments link the HIP to the control of food intake [74,75]. Finally, the PFC is responsible for higher-order cognitive processes related to attention, working memory, decision-making and planning [131]. The mPFC receives input from insular cortex regions that relay gustatory information [311], and mPFC inputs to the NAc have an important influence on NAc signalling [151,226]. As a common element among the NAc, AMY, HIP and PFC are the inputs of DA neurons originating in the VTA that together form the mesocorticolimbic DA pathway (Fig. 3).

The anatomical and functional division of the NAc into different subterritories, namely the shell and core, is well-recognized [368]. Pharmacological manipulation of opioid, cannabinoid, GABA, glutamate and MCH receptor signalling selectively in the NAc shell produces particularly robust effects on feeding [121,189,211] which is reflected by the convergence of neurotransmitter and peptide signals in this region. Consistent with its distinctive role in the regulation of feeding behaviour and food reward, the NAc shell is innervated by subcortical structures involved in energy homeostasis including the ARC, LH, VTA, nucleus of the solitary tract (NTS) and parabrachial nucleus (PBN) [369]. In turn, the NAc shell sends descending outputs to feeding-related sites such as the VP, VTA and LH [369].

With its reciprocal connections with the NAc, the LH serves as an important moderator between limbic motivational processes and motor output pathways (Fig. 3). A long line of neurophysiological and neuroanatomical research implicates the LH in the

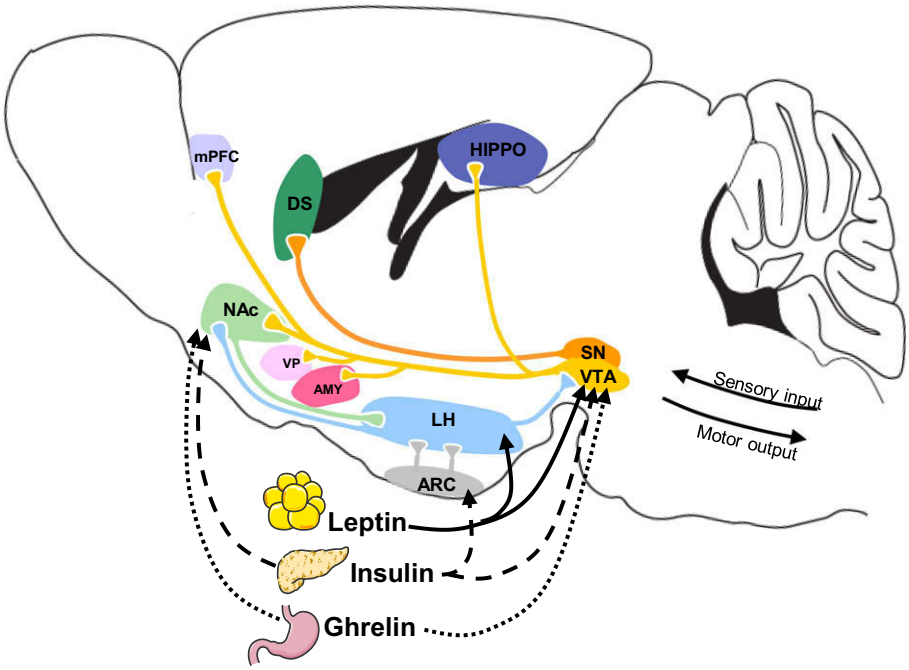

Fig. 3. Corticolimbic circuitry integrates metabolic information via multiple inputs. Present knowledge of the sites targeted by leptin, insulin and ghrelin to impact reward-relevant behaviour and circuitry. Leptin targets the VTA and LH neurons that project to the VTA [99,107,170,203], inhibits food intake when infused into these nuclei [170,203] and is important for regulating DA tone [107,170,203,287]. Insulin targets the VTA and striatum and reduces DA tone [99,206]. VTA insulin decreases MOR-induced feeding while ARC insulin inhibits sucrose responding [97,100]. Ghrelin targets VTA DA neurons [3,377], enhances DA tone [3,181,265] and increases food intake when administered to the VTA and NAc [3,236]. Midbrain DA neurons project to limbic and cortical sites that regulate emotion, cognition and learning. The NAc is well-positioned to assimilate information about emotion, cognition, metabolic state and gustation arising from AMY, mPFC and HIPPO, ARC, LH, VTA and hindbrain afferent inputs (not all depicted here). Corticolimbic nuclei send descending projections to basal ganglia motor outputs to convert motivation into behavioural actions. GABAergic medium spiny neurons of the NAc shell (feeding hotspot) also reach motor output pathways by way of LH neurons that are critical for NAc shell modulation of feeding behaviour.

regulation of energy homeostasis. LH cells can respond to the taste [240], sight [285] and smell [307] of food and receive gustatory afferents from the thalamus [86] and hindbrain [241]. Moreover, LH cells receive information about peripheral energy stores from hormones like leptin [85,148,203], nutrients signals such as glucose [248] and afferents originating from energy-sensing mechanisms in the ARC [84].

Among the important LH neuronal populations involved in the control of food intake are those expressing the orexigenic peptides orexin and MCH. MCH and orexin neurons innervate several regions including the NAc and VTA, respectively, and thus may establish another means whereby information about metabolic state and sensory modalities influence corticolimbic circuitry. Correspondingly, increased food intake by MOR [375] or GABA receptor [22] stimulation in the NAc shell appears to rely on projections between the NAc and the LH that stimulate orexin neurons. Moreover, orexin-1 receptor signalling in the VTA is an essential downstream mediator of the process whereby MOR stimulation in the NAc shell enhances high-fat feeding [375]. Thus, LH orexin neurons may be part of a striatal–hypothalamic–basal ganglia–striatal loop which controls intake of fatty foods. Finally, recent findings demonstrate the existence of a subpopulation of GABAergic LH neurons that express leptin receptors and project to the VTA. Direct leptin administration into the LH decreases food intake while increasing VTA TH expression and NAc DA content in *ob*/*ob* leptin-deficient mice that exhibit diminished TH expression in the VTA. Still much remains to be learned about the LH and the distinct connections and characteristics of its subdivisions [300,349]. The complexity of this heterogeneous area is also derived from the numerous fibers of passage coursing rostrally and caudally through more lateral portions of the LH that comprise the medial forebrain bundle (MFB) [238]. The MFB is a common locus for electrical stimulation that gives rise to rewarding self-stimulation behaviour. As will be discussed in the next section, studies of brain stimulation reward (BSR) implicate a subset of reward-related neurons located in or coursing through the perifornical LH in the regulation of energy balance.

4.2. Brain stimulation reward and energy balance

The landmark study of Anand and Brobeck in 1951 showing that bilateral electrolytic lesions of the LH resulted in a profound decrease in feeding, drinking and body weight likely inspired the view that the LH signals the rewarding properties of foods [13]. Thereafter, similar findings documented the reliable symptomology of LH electrolytic lesions which collectively became known as the LH syndrome. The significance of the LH was reinforced by demonstrations that electrical stimulation through the same LH electrode that could give rise to the BSR could also elicit a feeding response [167]. Furthermore, using conventional rate measures, self-stimulation of the LH in rats was shown to increase in response to acute food deprivation [78,215] and decrease following force feeding and spontaneous meal consumption in a manner resembling the influence of these manipulations on food intake [164,168]. Collectively, these findings encouraged the notion of the LH as a "feeding center" (see [35]).

Subsequent studies employing threshold measures (e.g., curve-shift method [224]) to determine changes in the reward effectiveness of BSR yielded different results. An acute period of food deprivation has little or no effect on rate-frequency thresholds for BSR [109,110]. In addition, while rats choose between gustatory stimuli and the LH stimulation in a manner that implies that the two rewards are being evaluated along a common dimension, there is compelling data that self-stimulation can be quite different from the signal generated by a rewarding piece of food [70–72]. When rats are given a choice between LH stimulation and either a sucrose

reward alone or a compound reward consisting of sucrose plus a fixed train of stimulation, Conover and Shizgal found that BSR remained stable as the sucrose solution accumulated in the gut whereas responding for the compound reward was substantially suppressed [71]. Therefore, models that proposed that rewarding LH stimulation is analogous to food reward are faced with paradoxical findings that manipulations that dramatically increase food intake largely fail to alter BSR in a similar manner.

There are several lines of evidence suggesting that stimulation of a subset of LH sites close to the fornix activates a stage of reward circuitry that contributes to the regulation of energy balance. Early investigations of Blundell and Herberg showed that response rates for rewarding LH stimulation increased with chronic food restriction and body weight loss only when the stimulating electrodes were located in the perifornical region of the LH [42]. Carr and Wolinsky obtained similar results when employing thresholds to measure changes in BSR over a period of food restriction and weight loss. In the same study these authors show that ICV injection of the non-selective opioid antagonist, naltrexone, reverses the potentiation of BSR by food restriction at perifornical sites [62]. The modulation of BSR by weight loss has been replicated several times [4,5,57,59,108–111], and depends on the site of stimulation in the LH [112]. These data suggest that stimulation of the LH recruits at least two anatomically and functionally distinct subpopulations of rewards neurons, one of which is linked to the regulation of body weight and can be activated by stimulating neurons residing in or coursing through the perifornical LH.

Through which circulating signals does food restriction and weight loss enhance the rewarding effect of perifornical stimulation? Fulton et al. investigated the impact of ICV leptin on the rewarding stimulation obtained from LH self-stimulation sites that are either sensitive or insensitive to weight loss [110]. Leptin suppressed the rewarding effect of the stimulation only at "restriction-sensitive" perifornical sites, thus leptin reversed the effects of weight loss on BSR. Conversely, leptin enhanced the rewarding effect of the stimulation at the majority of "restriction-insensitive" sites. These contrasting effects of leptin at restriction-sensitive and -insensitive sites are interpreted in terms of the different ways in which leptin can contribute to the regulation of energy balance [109,110,316]. On the one hand, leptin may suppress the rewarding effects of behaviours that promote energy intake while, on the other, augment those compatible with increased energy expenditure, such as physical activity. Along with leptin, the circulating levels of insulin also vary as a function of the amount of adipose tissue. Two reports by Carr and colleagues implicate insulin in the modulation of BSR by food restriction and weight loss. In one study they found that streptozotocin administration, a manipulation that decreases insulin levels, potentiated the rewarding effects of the stimulation [60]. Conversely, ICV administration of insulin attenuates the rewarding effect of the stimulation [61]. Leptin and insulin may alter BSR via their well-characterized influence on neuropeptide systems. However, while central CRH and NPY infusions altered food intake they largely failed to modulate BSR at restriction-sensitive sites [111,108]. Together, the data suggest that CRH and NPY are not intermediates in the process whereby leptin and insulin modulate the rewarding stimulation at restriction-sensitive sites, but do not exclude the possibility that other neuropeptides, such as AgRP and orexin, could be involved.

Collectively, the data demonstrate that food restriction, opioids, leptin and insulin alter a subset of reward-relevant circuitry in a manner that is consistent with their impact on behaviours that contribute to energy intake. However, it is not plausible that restriction-sensitive reward neurons produce a signal of that is generally related to hunger given that manipulations that increase the rewarding effects of food, including acute food deprivation, do not modulate BSR at restriction-sensitive sites [109,110]. As described by Shizgal et al., one possibility is that the restriction-sensitive subpopulation of reward neurons is tied to the regulation of non-ingestive behaviours that defend body weight, such as food hoarding [316]. Indeed, food hoarding behaviour is highly correlated with body weight, as rats loose weight they will hoard proportionally more food [56,91]. Moreover, food hoarding is not influenced by acute food deprivation nor NPY administration [54,56]. An alternative possibility draws on developments regarding the circuits and peptides affecting fat intake to suggest that the restriction-sensitive subset of reward neurons contribute to the rewarding properties of high-fat food. Consistent with this view is evidence that preference for high-fat food is modulated by manipulations similar to those affecting BSR at restriction-sensitive sites, including chronic food restriction and weight loss [306] and opioids [69,235]. These ideas remain speculative but provide interesting prospects for empirical investigation.

4.3. Dopaminergic correlates of feeding

Based on his classical studies in the early 1970s in which severe aphagia and adipsia was induced by 6-OHDA DA lesions, Ungerstedt proposed that the LH syndrome resulting from lesions of the LH is the consequence of damage to ascending DA pathways [345]. Later work demonstrated that the feeding and metabolic impairments could result from the loss of intrinsic LH neurons (see [35]), nonetheless, this early demonstration was the beginning of an extensive line of work investigating the impact of DA in feeding. Indeed, a central focus of much of the research on the neurochemical basis of feeding is the mesocorticolimbic DA pathway. To set the stage for evidence that DA neurons and their inputs are targets of hormones involved in energy balance, key findings regarding the physiological properties of DA neurons and their responses to feeding are discussed below.

There has been much research devoted to understanding the regulation of firing patterns of DA neurons and several influential findings have tied the activity state of DA neurons to specific coding and behavioural functions. DA neurons recorded *in vivo* are reported to exhibit three patterns of activity: an inactive state; a slow, single-spike state, known as tonic firing pattern; and a burst or phasic mode [135]. The tonic firing pattern of DA neurons results in relatively low and more diffuse extracellular DA levels and is driven by an intrinsic pacemaker [137], whereas phasic activity has been show to rely on afferent input to DA neurons [136] and to produce high synaptic DA concentrations which activate post-synaptic DA receptors [117,323]. Importantly, the phasic pattern of DA firing and release has been functionally tied to goal-directed behaviour and the prediction of rewards [302,303]. The dynamics of DA release in mesolimbic and nigrostriatal DA pathways are also influenced by D2-autoreceptors which provide negative feedback by rapidly inhibiting DA release [133]. Bearing in mind these and other characteristics, it is increasingly evident that striatal DA transmission is not a unitary phenomenon, but can be separated into distinct functional components based on DA terminal region and activity state.

DA transmission in the NAc has been linked exclusively with the consummatory rather than anticipatory aspects of feeding (e.g., [357]) and related to the amount of food ingested [219]. Nonetheless, the results of several studies suggest that DA firing and release is closely tied to novel food stimuli and/or to the responses and stimuli that are predictive of food reward. Using *in vivo* microdialysis to sample extracellular DA concentration, early studies of Hoebel and colleague found DA levels are elevated in the NAc during lever-pressing for food in food-restricted rats and DA release remains elevated during and after food consumption [158]. In other studies, DA release in the NAc is specifically associated with the instrumental response required to get access

to familiar food but not with food consumption [295], an effect that is more pronounced in the NAc shell region [321]. Bassareo and Di Chiara found that DA release is stimulated in the NAc shell during initial exposure and consumption of novel food but not during subsequent presentations, suggesting that DA release undergoes habituation to food stimuli [28]. These authors also find that DA is preferentially released into the NAc shell as compared to the core in response to unpredicted food, but following repeated exposure to food stimuli the DA response shows habituation only in the shell [29]. In a compatible manner, DA release is stimulated in the NAc shell only during conditions in which a food reinforcement is unpredictable [9]. Similar results have been obtained with single unit recordings whereby VTA DA neurons exhibit phasic firing in response to unpredicted food rewards [303]. However, once food is associated with stimuli that predict its availability, phasic DA activation is then triggered in response to these predictive stimuli [303].

Employing cyclic voltammetry which measures DA release over much shorter-time frames (100 ms) than microdialysis, Roitman et al. discovered that phasic DA released is stimulated in the NAc core in response to familiar sucrose-associated cues and peaks during lever-pressing responses for sucrose reward but returns to baseline during food consumption [281]. In another study that uses novel food stimuli, these investigators found that phasic DA release is triggered in the NAc shell during oral sucrose infusions which persisted during the consummatory phase [283]. In contrast, these authors report that intra-oral infusions of novel aversive stimuli (quinine) produced significant decreases in DA release. In a reverse manner, a subset of NAc neurons are inhibited by tasting a sucrose solution whereas another subset are excited by quinine to suggest that behavioural responses to rewarding and aversive stimuli are anatomically divided at the level of the NAc and its outputs [282]. Interestingly, NAc DA release and the activity of NAc neurons in response to sucrose ingestion are not contingent on functional taste transduction suggesting that DA release can be modulated by post-ingestive controls that condition feeding behaviour [77,304].

DA release has been measured during conditions of feeding in DA terminal regions other than the NAc, although these reports are less common. DA release is elevated following feeding in the DS but not the HIP in food deprived rats [217]. In contrast, another study found no increase in extracellular DA release in the DS during and following food intake [65]. Consumption of a novel food stimulates DA release in the mPFC in non-deprived rats [28] and mPFC DA release has been shown to increase just prior to the delivery of predictable and familiar food rewards but not during food consumption [271]. Moreover, mPFC DA release has been shown to exert an important inhibitory influence on NAc DA release and food-reinforced responding [226]. Finally, there is a strong correlation between the magnitude of DA release in the mPFC and performance on a food-associated memory task [255].

As illustrated by the studies above, there are different DA responses in the NAc shell versus core which reflect the functional differences between these compartments and their inputs [368]. DA release is elevated in the NAc and mPFC during both appetitive and consummatory phases of feeding for novel food, but phasic DA release in the NAc shell is no longer triggered during food consumption upon subsequent presentation of the food. Thus, in the case of familiar foods, DA release in the NAc and mPFC appears to be preferentially linked to predictive instrumental responses or conditioned stimuli rather than actual food consumption. DA release in the mPFC appears to also play a role in the retrieval of cue-associated memories that correctly guide animals towards food. These finding are consistent with the view that DA serves as a teaching signal to influence future commerce with food stimuli. Consistent with these data is the wealth of evidence showing that DA is critical for long-lasting cellular changes in the striatum, including homeostatic neuroadaptations [175], synaptic plasticity [197,278] and structural modifications [278]. In particular, there have been great advancements in our understanding of the molecular mechanisms in the NAc that correspond to behavioural adaptations in response to rewarding drugs of abuse in which DA is purported to play a central role [175]. How these molecular adaptations figure in the regulation of food reward is beginning to be revealed.

4.4. Impact of metabolic signals on reward circuitry

Of the objectives that must be met for an animal to survive the goal of maintaining adequate energy levels occupies a commanding position. The energy state of the animal not only influences behaviours oriented towards attaining and consuming food but also has direct bearing on all other behavioural actions necessitating energy expenditure. Thus, it is not surprising that the brain comprises numerous mechanisms by which it can sense the status of energy fuels so that it may adjust sensory, autonomic and behavioural systems to efficiently meet energy demands. The study of the pathways and mechanisms by which hormones and nutrient signals influence food intake has substantially advanced our knowledge of the CNS controls of energy homeostasis. The view that sensing of peripherally-derived energy signals is the exclusive function of hypothalamic and hindbrain cells has been modified by several lines of evidence indicating that hormonal signals, like leptin and insulin, target neuronal populations throughout the brain [85,152,232,308] to affect sensory modalities, biological rhythms, memory and reward-relevant processes.

The modulation of reward circuitry by leptin has been described in both rodents and humans. Leptin inhibits the rewarding effects of LH self-stimulation [109,110], goal-directed behaviour for food [96,98], food-deprivation induced heroin seeking [310] and enhances the locomotor-activating effects of amphetamine [107,150]. Shedding light on the sites that may mediate such effects, leptin receptors are localized to midbrain DA neurons [99,170] and leptin administration decreases basal and feeding-evoked extracellular DA levels in the NAc shell [198]. Demonstrating a direct action of leptin on DA neurons, Hommel et al. report that infusion of leptin in the VTA activates STAT3 in DA neurons and decreases food intake [170]. Conversely, conditional leptin receptor knockdown in the VTA increased food intake and locomotor activity. As a potential mechanism mediating the influence of leptin on feeding, these authors demonstrate that systemic leptin administration or direct leptin application to the slice bath decreases the tonic firing of VTA DA neurons. Complementing these findings, Fulton et al. reported that leptin activates STAT3 in DA and GABA neurons of the VTA and that a subset of pSTAT3-positive neurons project to the NAc core and/or shell [107]. Obese leptin-deficient *ob*/*ob* mice showed substantially reduced locomotor responses to amphetamine and failed to sensitize to repeated amphetamine administration, impairments which were restored by peripheral leptin infusion [107]. As an explanation for the diminished locomotor response to amphetamine, stimulation-evoked DA release in the NAc shell was significantly reduced in *ob*/*ob* mice along with DA and TH content in the NAc. This finding is in agreement with evidence of Roseberry et al., showing that cocaine-induced somatodendritic DA release, as measured by D2 autoreceptor inhibitory post-synaptic potentials, is reduced in *ob*/*ob* mice [287]. These authors also provide evidence to suggest that impaired vesicular packaging of DA contributes to reduced DA release in *ob*/*ob* mice. Finally, Leinninger et al. recently demonstrated that infusions of leptin into the LH reduce food intake and increase VTA TH and NAc DA content in *ob*/*ob* mice. These investigators identify a novel subpopulation of GABAergic LH neurons that

innervate the VTA and are functionally targeted by leptin, and thereby reveal a means by which leptin may modulate DA availability in the mesoaccumbens pathway.

Human imaging research draws attention to the NAc as a locus mediating the impact of leptin on food reward. Farooqi et al. demonstrated that NAc activation, as measured by functional magnetic resonance imaging (fMRI), is positively correlated with affective ratings of visual food stimuli in fed and fasted leptin-deficient humans [93]. Following leptin treatment the association between NAc responses and affective reactions remain in the fasted conditions but disappear in the fed state. These findings do not implicate changes in leptin signalling to altered DA tone in the NAc, however they pinpoint the NAc as a site that integrates information about leptin signalling, metabolic state and affective responses for food. Collectively, the rodent and human studies demonstrate that leptin modulates feeding behaviour via direct actions in the VTA and LH, modulates affective responses for food that coincide with NAc neural activity and regulates DA signalling and plasticity in the VTA to NAc pathway. On the one hand, leptin reduces the tonic firing of DA neurons, while on the other, leptin is important for DA availability, packaging and release. While these studies implicate the mesolimbic DA system and inputs from the LH as regions involved in leptin action, additional investigations that measure reward (e.g., operant responses for food), in particular, are required in order to identify the neurons and mechanisms involved.

Insulin receptors are abundantly expressed throughout the brain, including the striatum and midbrain, and insulin is involved in the modulation of reward-relevant processes [100]. Figlewicz et al. identified insulin receptors on DA neurons of the VTA and SN [99]. These investigators report that insulin and leptin administration to the VTA increases immunoreactivity for phosphatidylinositol-3 (PI3) kinase, a signalling molecule activated by insulin and leptin receptor signalling [100]. In addition, they show that VTA infusion of insulin and leptin attenuates the feeding response induced by opioids in this region. Earlier studies demonstrate the ability of insulin to decrease DA release in striatal terminal regions [221] whereas streptozotocin-induced hypoinsulinemia increases striatal DA release [51]. Central insulin administration augments DAT mRNA levels in the SN and VTA [102] whereas DAT mRNA levels are diminished during reduced insulin signalling [101]. Carvelli et al. demonstrate the functional actions of insulin to increase dopamine reuptake and facilitate the cell surface expression of DAT *in vitro*, and they provide evidence that these effects are mediated by PI3-kinase signalling [63]. Moreover, this group found that amphetamine-stimulated DA release in the striatum is impaired in insulin-deficient rats whereas insulin microinfusion into the striatum recovers this PI3-kinase mediated effect [206]. Together, the data suggest that insulin suppresses striatal DA tone by increasing DA clearance. It remains to be determined whether insulin directly influences DA neurotransmission, although this possibility is supported by the observation that insulin interacts with opioids in the VTA to decrease food intake. Interestingly, opioids down-regulate the insulin-receptor substrate-2 (IRS2) thymoma viral proto-oncogene (Akt) pathway in DA neurons of the VTA to regulate the cellular and behavioural effects of morphine [292], thus activation of IRS2-Akt pathway by insulin may be responsible for attenuating opioid-induced feeding.

Like leptin and insulin, the gut-derived hormone ghrelin modulates reward-relevant behaviour and targets DA neurons of the VTA. Ghrelin binds to growth hormone secretagogue receptors (GHSR) to stimulate food intake and adiposity [343]. GHSR receptors are expressed in several brain regions including the VTA [3,144,377]. Peripheral ghrelin enhances the locomotor-activating effects of cocaine [355] and conditioned place preference [180]. Naleid and coworkers discovered that ghrelin injected in either the VTA or NAc increases food intake in rats [236]. This orexigenic effect of ghrelin may be due to its ability to stimulate DA release as central ghrelin administration potentiates extracellular levels of DA in the NAc [181]. Illustrating the direct action of ghrelin on VTA DA neurons, Abizaid and coworkers demonstrated that ghrelin binds to VTA cells and increases DA firing [3]. The increase in DA firing is associated with ghrelin-induced increases in the number excitatory synaptic inputs and decreased inhibitory inputs to VTA DA neurons observed by these authors. These investigators also find that ghrelin increases DA turnover in the ventral striatum and stimulates food intake when administered into the VTA. Likewise, NAc DA release is elevated following direct VTA infusion of ghrelin [182] whereas recent work suggests that peripheral ghrelin stimulates DA release exclusively in the NAc shell and not the core [265]. Finally, ghrelin is reported to enhance human cerebral responses to visual food cues in the AMY, insula, orbitofrontal cortex (OFC) and striatum as measured by fMRI [214]. In this study, ghrelin treatment increased hunger ratings as a function of the degree of activation in the AMY and OFC to suggest that increased motivation for food induced by ghrelin treatment is mediated by processes encoded in these regions. Collectively, the rodent and humans studies strongly implicate ghrelin in the modulation of the neural networks controlling motivation.

Human imaging studies have offered great insight into the neural responses associated with motivation for food in different metabolic states. Investigating the neural responses that are predictive of later food consumption, Batterham et al. measured neural activity in response to the anorexigenic gut hormone PYY [32]. These investigators found that when circulating PYY levels were low, as during the fasted state, changes in neural activity in the hypothalamus were predictive of later food intake. In contrast, changes in activity of the caudolateral OFC predicted feeding when PYY levels were high [32]. These results demonstrate how a postprandial satiety factor can switch neural controls of food intake from hypothalamic to corticolimbic regions and thereby implicate corticolimbic processes in excessive caloric intake. Consistent with this idea, Volkow, Wang and colleagues provide evidence of reduced striatal D2 dopamine receptor binding in obese humans to suggest that there is reduced DA tone in these individuals [352,353]. Correspondingly, DS activation is attenuated in obese humans, an effect that is even more pronounced in individuals with the A1 allele of Taq1A polymorphism which is associated with the D2 receptor gene and reduced striatal DA signalling [328]. Interestingly, the results of several studies in humans [328,352,353] and rodents [76,107,119] link diminished striatal DA signalling to hyperphagia and obesity. Thus, while the consumption of palatable foods may stimulate striatal DA neurotransmission, genetically-derived and/or diet-induced impairments in the amount of DA available for release may be a factor promoting increased caloric intake.

As summarized in Fig. 3, information regarding the status of energy reserves is being relayed to corticolimbic sites by the actions of leptin, insulin and ghrelin to modulate DA and/or striatal cell signalling. It is possible that these and other hormones affect corticolimbic controls of food motivation by also signalling in upstream neural pathways in the hypothalamus and hindbrain. Indeed, recent data shows that leptin targets LH-VTA projection neurons to increase DA content [203]. Moreover, insulin administration in the ARC suppresses sucrose-reinforced instrumental responding [97]. There remains several questions concerning the precise mechanisms by which metabolic and central signals modulate DA activity states and release, which corticolimbic targets and signalling molecules are affected and how these processes relates to immediate and long-term behavioural changes. It also remains to be determined whether or not leptin, insulin and

ghrelin target the same DA neuronal subpopulations and, if so, if there are functional interactions between their respective receptor signalling pathways. Finally, it is not yet clear to what extent the signalling of these hormones in midbrain and limbic sites specifically influence the appetitive and/or consummatory aspects of feeding. It could well be that hormonal sensing at these loci has more general actions to orient attention and motivation toward behavioural actions that are compatible with the current energy state of the animal.

5. Conclusion

The reward efficacy of food is not only influenced by fluctuations in metabolic status but also by the palatability and post-ingestive consequences of foods. Thus, food reward can be enhanced by the sensory qualities of food independent of energy demands and may provide a major basis for overeating and weight gain. One can deduce from such observations that neural processes regulating motivation for food can override signals of satiety and adequate energy fuel and/or that impaired responses to such signals may develop that promote excessive food intake. There is evidence for both propositions. Palatable high-fat and -sugar foods can generate neural responses in corticolimbic circuitry that strengthen future behaviour directed towards these foods. Such mechanisms loom large in environmental settings inundated by cues that summon up memories of eating and remind us how, where and when we can get access to food. On the other hand, a high-fat diet and resulting elevations in circulating adiposity signals and nutrients can impair signalling mechanisms in the mediobasal hypothalamus and thereby weaken catabolic responses [231,350]. Such impaired responses to anorexigenic signals may represent another means whereby motivation for food may be increased by high-fat and -sugar foods.

Future research will benefit from considering the important influence of environmental variables and their interaction with biological and genetic components on the type and amount of food we choose to eat. For example, epidemiological evidence suggests that poor quality food options in conjunction with limited economic resources contribute to increased risk for obesity in socioeconomically disadvantaged regions [104]. Environmental settings have been modeled in rodent experiments by manipulating the availability of food alternatives. In rats it has been shown that increasing the number of containers of high-fat and -carbohydrate food in the cage elevates caloric intake relative to conditions where fewer containers, but equal amounts, of these foods are available [339]. Similarly, economic conditions are modeled in rodent studies by influencing the price (response requirement) of food and/or limiting the context in which food alternatives are available [173,313]. For instance, appetite for fat solution in rats is greatly affected by the price of the fat reinforcer, especially when other palatable food alternatives are available [106]. Thus, in environments in which the cost of high-fat and sugar foods is relatively low and financial resources are limited, it is increasingly evident that we need to unravel the neural mechanisms that process the rewarding effects of palatable foods in the context of modern social and economic climates.

Neurons in the VTA, LH and ARC are well-positioned to relay metabolic information to corticolimbic controls, but clearly more remains to be uncovered about the pathways and signalling molecules by which this information is conveyed. Metabolic information is channelled to the striatum, especially the NAc shell, where DA, Ach, opioids and endocannabinoids signals interact to modulate affective and goal-directed responses for food. Finally, great headway has been made in determining the molecular mechanisms tied to long-lasting behavioural responses for drug rewards and recent work is shedding light on similar molecular underpinnings for energy-rich food (e.g., [332]). Despite the complexity of these circuits, the use of cell-specific gene targeting, tract tracing, pharmacological and electrophysiological approaches along with precise behavioural measures offers great promise that future work will continue to tease apart the pathways and mechanisms responsible for the rewarding effects of food.

Acknowledgements

The author thanks Thierry Alquier, Vincent Poitout and Marc Prentki for valuable input on the manuscript.

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