Review

Feelings about food: the ventral tegmental area in food reward and emotional eating

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Overconsumption of high caloric food plays an important role in the etiology of obesity. Several factors drive such hedonic feeding. High caloric food is often palatable. In addition, when an individual is sated, stress and food-related cues can serve as potent feeding triggers. A better understanding of the neurobiological underpinnings of food palatability and environmentally triggered overconsumption would aid the development of new treatment strategies. In the current review we address the pivotal role of the mesolimbic dopamine reward system in the drive towards high caloric palatable food and its relation to stress- and cue-induced feeding. We also discuss how this system may be affected by both established and potential anti-obesity drug targets.

Drivers of hedonic feeding

Feeding helps maintain energy balance, but is also pleasurable, especially when it concerns high caloric food. 'Hedonic' feeding occurs when a sated individual consumes food mainly because of its palatability (meaning it is a tasty reward), rather than for nutritional need. This behavior can be triggered by environmental factors such as food cues (e.g., advertisements) or by stressors that lead to negative emotions (i.e., stress-eating). In healthy individuals, emotions and food cues are triggers for initiation of feeding, but this is especially so in obese individuals [1,2]. Therefore, a better understanding of the neural networks that encode the drive to overeat is required for adequate obesity treatment. In the current review we describe the extensive role of the ventral tegmental area (VTA) in hedonic feeding. The VTA is an integrator of peripheral, hypothalamic, mid/hindbrain, limbic, and cortical information [3]. Functionally it encodes motivation for palatable food, and stress- and cue-induced feeding. These three factors, mediated by distinct, but partly overlapping neural circuits in which the VTA is embedded, contribute to the difficulty of an individual to adequately limit food intake.

Energy balance and reinforcing properties of food

The midbrain dopamine system consists of subpopulations of dopamine neurons, each playing specific roles. Dopamine neurons in the substantia nigra have been implicated in motor control and project to the (dorsal) striatum. More medial in the VTA, a subgroup of heterogeneous dopamine neurons are implicated in motivation, reward, and aversion and project to the nucleus accumbens (NAc), ventral pallidum (VP), prefrontal cortex (PFC), amygdala, and hippocampus [4].

Although the VTA also has GABAergic and glutamatergic projections [5–7], the most studied output in relation to feeding is dopamine. Dopamine signaling does not mediate the pleasurable sensation of food *per se* [8]; instead, it is especially involved in the expenditure of effort to obtain desired food, as well as in the detection of unexpected food reward and its coupling to predictive cues [8–12]. We now further address how different inputs and transmitter systems in the mesolimbic dopamine systems can encode information pertaining to some of these facets.

Signals from the gastrointestinal tract act on the VTA

The VTA receives direct information from the gastrointestinal tract (Figure 1). Most notable, the stomach peptide ghrelin acts on the VTA, where ghrelin receptors (GHSRs) are expressed both on dopamine and non-dopamine neurons [13,14]. Ghrelin directly increases the firing rate of dopamine neurons in the VTA in a GHSR-dependent manner [13] and leads to elevated dopamine levels in the NAc [15]. Ghrelin also elevates cholinergic input from the laterodorsal tegmental nucleus (LTDg) to the VTA [15], presumably to dopamine neurons that project to the NAc shell [16]. This ghrelin-modulated LDTg input is indeed important for ghrelin-induced accumbal dopamine release.

Ghrelin signaling in the VTA increases intake of palatable food (peanut butter) more than chow in sated animals [17], but also enhances motivation for lever presses for palatable sucrose [18]. Interestingly, the effects of intra-VTA ghrelin on chow intake and motivation for sucrose

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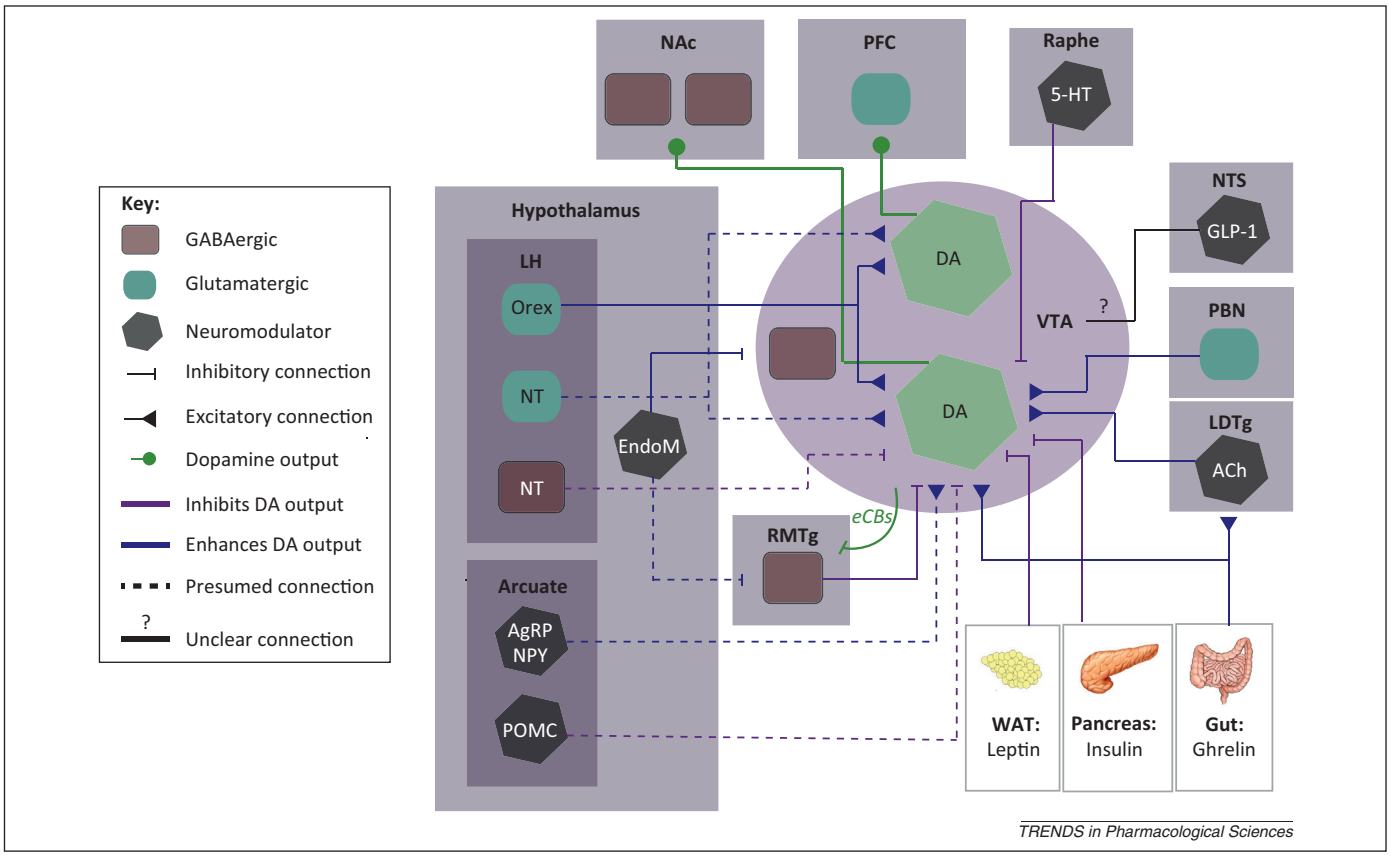

Figure 1. Encoding of drive for palatable food by the mesolimbic dopamine system. Different subsets of ventral tegmental area (VTA) neurons receive multiple inputs that allow it to encode motivation for palatable food. Information on energy balance comes from white adipose tissue (WAT), the pancreas, and the gut. From the lateral hypothalamus (LH) orexin and neurotensin (NT) are sent, and from the arcuate nucleus, presumably agouti-related peptide (AgRP), neuropeptide Y (NPY), and melanocortins (MCs) from proopiomelanocortin (POMC) neurons. Endomorphin (EndoM) comes from other hypothalamic regions. In the mid/hindbrain, the nucleus of tractus solitarius (NTS) provides glucagon-like peptide 1 (GLP-1). Signals also arise from the parabrachial nucleus (PBN), the raphe nuclei, and the rostromedial (RMTg) and laterodorsal tegmentum (LDTg), the latter also releases acetylcholine (ACh). Main output from the VTA (green) includes projections to the nucleus accumbens (NAc) and prefrontal cortex (PFC), and local release of endocannabinoids (eCBs). For clarity, not all connections between nuclei are shown, only those directly impacting on the VTA and currently considered to be involved in (food) reward processes.

have different underlying mechanisms. The enhanced motivation for sucrose requires both opioid signaling in the VTA, and D1 and D2 receptor dopamine signaling in the NAc [19,20]. By contrast, the increased chow intake requires neither opioids in the VTA nor dopamine in the NAc [19,20]. This difference potentially reflects an important distinction between effort-based intake of (palatable) food and intake of freely available (non-palatable) food [21].

Energy supply signals act on the VTA to regulate palatable feeding

The VTA may be sensitive to alterations in available bodily energy stores. A key mediator in this process is leptin, an adipocytokine that becomes elevated with more stored white adipose tissue (and thus more stored energy), and which suppresses hunger in part by acting on hypothalamic circuitry [22]. However, leptin receptors (LepRs) are also expressed on VTA dopaminergic and GABAergic neurons [23,24]. Leptin directly hyperpolarizes VTA dopamine neurons and decreases their neuronal firing frequency both in slices and *in vivo* [24,25]. Moreover, leptin suppresses glutamatergic input onto VTA dopamine neurons [26]. LepR-containing VTA dopamine neurons have been shown to project to the central amygdala (CeA) [27]. However, LepRs, presumably those in the VTA, also play an important role in regulating dopamine levels in the NAc and have also been suggested to project there [28]. Functionally, leptin suppresses the incentive value of food and other rewards [29,30]. Infusions of leptin into the VTA suppresses food intake [24,31]. Contrarily, LepR knockdown in the VTA results in increased intake of novel palatable foods, such as sucrose and high-fat chow [24]. Interestingly, selective removal of LepRs from dopamine neurons does not affect body weight or intake of either chow or palatable food. Instead, it results in increased anxiety levels due to enhanced dopamine signaling at D1 receptors (D1Rs) in the CeA [32]. Overall, these findings suggest that the effects of leptin on food intake that involve the VTA are potentially mediated by indirect action on the dopamine system. Instead, direct action of leptin on VTA dopamine neurons is likely to reduce anxiety levels.

The VTA also contains insulin receptors [23]. Insulin mildly increases the firing rate of half of the dopamine neurons in the midbrain [33]. Systemic insulin administration enhances dopamine release in the NAc [128]. However, insulin in the VTA reduces local dopamine release within the VTA itself by increasing the activity of the dopamine transporter [34]. Insulin signaling in the VTA reduces the drive for induced intake of palatable food [34,35]. Insulin receptors in the dopamine system may

also contribute to energy balance. Mice that selectively lack insulin receptors in catecholamine-expressing neurons (which includes dopamine neurons) exhibit increased food intake, body weight, and adiposity [33].

Hypothalamic inputs and peptides affecting VTA-mediated feeding

The hypothalamus serves a critical role in feeding and has strong connections with the VTA, also supplying it with several neuropeptides. For instance, melanocortins (MCs) arising from the hypothalamic arcuate nucleus act on the MC3 and potentially the MC4 receptor in the VTA [36,37]. This probably occurs mainly through a process of volume transmission, because direct synaptic contacts between the arcuate nucleus and VTA dopamine neurons appear to be largely absent [3]. When injected in the VTA, the MC3/4R agonist α-melanocyte stimulating hormone (α-MSH), and the MC3/4R inverse agonist agouti-related peptide (AgRP) affect dopamine turnover in target areas [38,39]. Moreover, AgRP neurons in the arcuate nucleus coexpress neuropeptide Y (NPY), which can act on NPY receptors on VTA dopamine neurons to increase dopamine release in the NAc [40]. Both MCs and NPY serve a potent role in intake of both palatable and standard food, and regulate motivated behavior for food [41,42]. However, it is largely unclear for the MCs whether they do so by acting on the VTA. By contrast, NPY signaling in the VTA at the Y1 receptor appears to be required for the enhanced chow intake, but not the enhanced motivation for sucrose after intra-VTA ghrelin signaling [19]. Arcuate proopiomelanocortin (POMC) and AgRP/NPY neurons are also sensitive to a variety of circulating appetite hormones [43,44]. Thus, hormones such as leptin, ghrelin, peptide YY (PYY), and glucagon-like peptide 1 (GLP-1) may affect dopamine neuronal activity via arcuate afferents to the VTA.

The hypothalamus also serves as a source for opioids (e.g., endomorphins) that act on μ-opioid receptors (MORs) in the VTA [45]. In the midbrain, MORs are located on GABAergic neurons in the VTA and also on GABAergic neurons in the rostromedial tegmental nucleus (RMTg), both of which project to dopamine neurons [4,46,47]. Infusion of opiates in the VTA enhances dopamine signaling in the NAc and PFC [48]. At least for the local GABAergic neurons in the VTA it has been shown that their activation inhibits palatable feeding [46]. The activation of MORs on these GABAergic neurons hyperpolarizes them, thereby disinhibiting VTA dopamine neurons [49,50]. Direct infusion of MOR agonists in the VTA induces hedonic feeding [35,51,52], whereas intra-VTA infusion of an opioid receptor antagonist reduces sucrose intake [53]. The effect of MOR activation in the VTA on feeding requires D1R as well as opioid signaling in the NAc shell [51].

Orexin, which is provided by neurons in the lateral hypothalamus (LH), is another hypothalamic feeding signal that acts in the VTA [54,55]. Orexin typically excites dopamine neurons via orexin 1 and 2 receptors located on VTA dopamine neurons themselves, although they are also present on non-dopamine neurons [56]. Orexins also enhance glutamatergic transmission to VTA dopamine neurons [57]. Infusion of orexin in the VTA enhances dopamine signaling in the NAc [129] and the PFC [130]. Orexins in the VTA play an important role in hedonic feeding, because they serve as a crucial intermediate step when hedonic feeding is evoked by enhanced opioid signaling in the NAc [58]. Specifically, enhanced MOR signaling in the NAc shell disinhibits orexin neurons in the LH, which send an important input to the VTA to trigger high-fat feeding [58]. Orexin neurons also respond to ghrelin [59], suggesting that appetite hormones may affect dopamine neuron activity indirectly via LH orexin afferents to the VTA.

Finally, there is a complicated interplay between neurotensin (NT) and the dopamine system, in which leptin also plays an important role. VTA dopamine neurons express NT1 receptors [60] and NT increases VTA dopamine neuron activity [61] Also, intra-VTA infusion of NT elevates dopamine signaling in the NAc [62] and the PFC [63]. Aside from these direct effects, there is also a hypothalamic projection from both GABAergic and glutamatergic neurons to the VTA that are probably able to co-release NT [64–66]. With regard to GABAergic NT-expressing positive neurons in the LH, it is known that they contribute to food-related behavior. These neurons express LepRs and synapse both directly on VTA neurons and potentially indirectly also via LH orexin neurons [65,66]. Leptin signaling (e.g., during satiety or exogenous application) directly excites these NT GABA neurons, resulting in silencing of LH orexin neurons, but intriguingly also in enhanced dopamine output of the VTA to the NAc [65]. In chow-fed mice, interfering with leptin receptors in these NT neurons slightly increases food intake and body fat [66]. It remains to be determined if these neurons also serve a role in hedonic feeding.

Mid-hindbrain inputs and peptides affecting VTA-mediated feeding

Taste information can be rapidly relayed to the VTA by a direct projection from the nucleus of the tractus solitarius (NTS) [67], which receives gustatory information from several cranial nerves [68,69] (Figure 1). The afferent vagal nerve is sensitive to a variety of gastrointestinal hormones and provides glutamatergic input onto NTS neurons. These afferents indirectly affect VTA neuronal activity via the NTS, which projects directly to the VTA, but also indirectly via, for instance, the parabrachial nucleus (PBN). A population of NTS neurons expresses the satiety hormone GLP-1 and sends a direct projection to the VTA [67,70]. This may be the main source of GLP-1 in the VTA, because it is unclear whether the GLP-1 produced in the intestine has a sufficiently long half-life to reach the central nervous system [71]. Although the behavioral profile (see below) associated with GLP-1R signaling in the VTA suggests that this signal reduces VTA dopamine output, no study has currently shown this. In contrast with this, GLP-1R stimulation in the VTA increases glutamatergic signaling onto dopamine neurons (although without a noticeable effect on the firing rate) and elevates levels of tyrosine hydroxylase (TH) [72]. The behavioral profile of GLP-1R signaling seems somewhat contrary to this. A GLP-1 receptor analog reduces palatable food intake and body weight, largely by acting on GLP-1Rs in the VTA [72]. Accordingly, local stimulation of GLP-1Rs in the VTA reduces intake of both sucrose and high-fat food, whereas

it only reduces chow intake when higher doses of agonist are used [67,73]. Moreover, GLP-1R stimulation in the VTA reduces the amount of effort willingly expended for sucrose [73], and shifts food choice more towards chow rather than palatable food [67]. In summary, there appears to be a discrepancy between the effects of GLP-1R stimulation in the VTA on physiology and behavior. Further studies will be required to address the effects of GLP-1R on dopamine signaling in target areas, in relation to the behavioral effects.

Another important relay is the PBN, which directly projects to dopamine neurons in the VTA [3]. From the PBN, putative glutamatergic projections target both dopamine and non-dopamine neurons in the VTA [74]. Silencing the PBN reduces the firing rate of VTA dopamine neurons [74], and the integrity of the PBN is required for the enhanced dopamine signaling in the NAc induced by palatable food [75]. The PBN is also one of the inputs to the VTA sensitive to cannabinoids, because the cannabinoid 1 receptor (CB1R) is present on both neurites and somata. Activation of CB1Rs in the PBN stimulates palatable (but not standard) food intake [69]. Cannabinoids also play an important role in the VTA when it comes to hedonic feeding. Endocannabinoids are synthesized by dopamine neurons and act in a retrograde manner to modify the strength of GABAergic and glutamatergic synaptic inputs, presumably mainly disinhibiting dopamine neurons [50,76–78]. Cannabinoid signaling in the VTA is a crucial driver of palatable food intake. Intra-VTA infusion of a CB1R agonist increases feeding in sated mice [79]. Moreover, local interference with CB1R signaling in the VTA reduces palatable feeding [79]. Such interference also completely blocks the increase in food intake induced by a peripherally administered CB1R agonist [80]. There is also evidence that CB1R activity in the VTA is enhanced after exposure to palatable food [81].

Another structure involved in palatable feeding is the serotonergic raphe nucleus, which sends a strong projection to the VTA [3]. The serotonin 2C receptor is present on both dopaminergic and GABAergic VTA neurons [82] and agonists for this receptor reduce dopamine output to the NAc [83]. Systemic administration of a serotonin 2C receptor agonist reduces the motivation for palatable food [84]. When such an agonist is directly infused in the VTA, this also reduces motivation for food pellets [85]. Overall, it is very plausible that serotonin signaling in the VTA, perhaps particularly at the serotonin 2C receptor, has an important role in hedonic feeding that needs to be investigated further.

Stress-induced palatable feeding

In response to stressors, humans often overconsume palatable food (comfort feeding) and tend to gain weight as a result [86]. This makes stress feeding a serious risk factor for the development of obesity. Under conditions of chronic stress, animals also overconsume palatable food (as opposed to a typical hypophagy observed for non-palatable food) [86]. The dopamine system and its output to regions such as the PFC and amygdala play an important role in stress-induced palatable feeding behavior [87–89]. We now discuss how stress information might be encoded in the VTA and how this is relevant for stress-induced palatable feeding. A summary of the key inputs that are involved is shown in Figure 2.

Stress hormones affecting VTA-mediated feeding

The stress hormone corticosterone directly acts on the VTA, where glucocorticoid receptors are present in approximately 50–60% of dopamine neurons [90,91]. Corticosterone infusion in the VTA enhances dopamine levels in the NAc [92]. Although corticosterone also enhances dopamine levels in the PFC, it does so by acting on glucocorticoid receptors in the PFC rather than in the VTA [93]. There is a role for corticosterone in hedonic feeding. Adrenalectomized rats (which therefore lack corticosterone) do not consume saccharin solution, but do so when they receive corticosterone replacement therapy [94]. The effects of corticosterone on feeding may be mediated indirectly, for instance, via affecting glucose metabolism. However, it may also directly act on dopamine circuitry. Stress exposure enhances glutamatergic drive onto VTA dopamine neurons, an effect dependent on both glucocorticoid and NMDA receptors [95]. Glucocorticoid secretion also enhances motivation for highly palatable food [96], although it remains to be determined whether it does so by acting at the level of the VTA.

The stress hormone corticotropin-releasing factor (CRF) also acts directly in the VTA, where CRF1 and CRF2 receptors occur on both dopaminergic and non-dopaminergic cells [40,97]. CRF increases the firing frequency of most VTA cells [40,98]. Intra-VTA CRF decreases dopamine metabolism in the PFC [99]. CRF can enhance dopamine levels in the NAc by enhancing specific synapses on the VTA [100]. NAc dopamine is also elevated by direct effects of CRF in the NAc, but only when an animal is not stressed [101]. There are several sources of CRF in the VTA: the hypothalamic–pituitary–adrenal (HPA) axis at the level of the paraventricular nucleus (PVN), the bed nucleus of the stria terminalis (BNST), and the CeA [102]. Within the BNST both glutamatergic and GABAergic neurons innervate non-dopaminergic and medially located dopaminergic VTA neurons [103], the latter of which presumably project to the PFC and are implicated in aversive processes [16]. It is known that the BNST plays an important role in hedonic feeding. Activation of GABAergic BNST neurons that project to glutamatergic neurons in the LH results in voracious feeding, especially of palatable food [104]. Whether CRF neurons in BNST projecting to the VTA play a role in stress feeding has not yet been determined, however. Interestingly, CRF in the CeA itself, rather than in the BNST [105], plays a role in hedonic feeding [105,106]. For example, interference with CRF signaling in the CeA reduces the overconsumption of palatable food, while not affecting the co-occurring reduced consumption of chow [105]. There is some evidence that this hypophagia for chow could instead be VTA-mediated. A recent study showed that CRF in the VTA reduced motivation for food and reduced dopamine release in the NAc core [100]. This finding implicates a role for CRF signaling in the VTA to reduce feeding during stress for standard food during hunger. However, it remains to be addressed whether VTA CRF signaling also contributes to stress-induced overconsumption of palatable food, and which region(s) would provide(s) that signal.

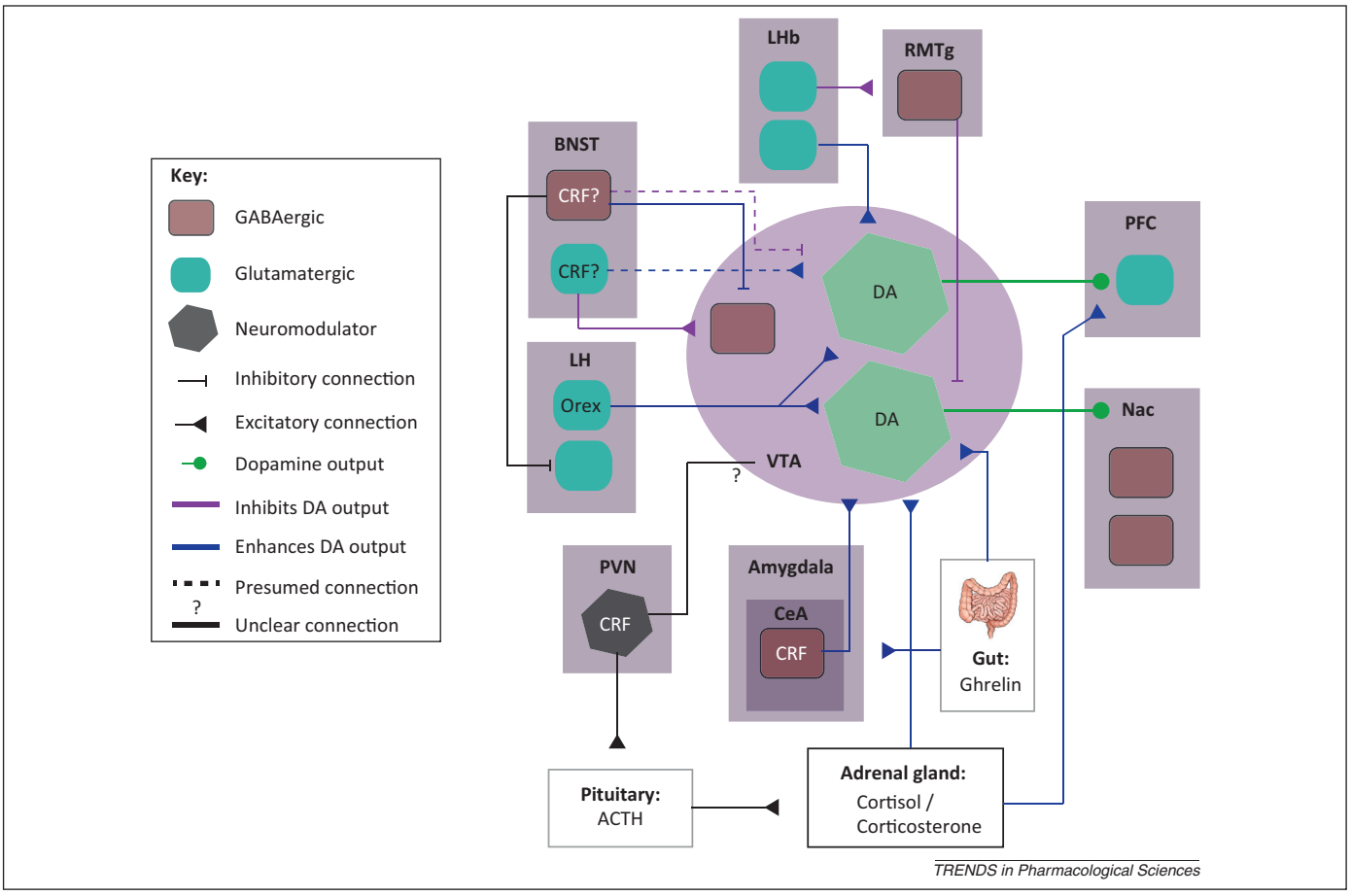

Figure 2. Encoding of stress-induced feeding by the mesolimbic dopamine system. The ventral tegmental area (VTA) is in close contact with the hypothalamic–pituitary–adrenal (HPA) stress axis. It directly receives information from stress hormones, such as corticosterone/cortisol, and corticotropin-releasing factor (CRF). Moreover, feeding peptides such as orexin and ghrelin, which can directly impact on the VTA, serve important functions in the stress response. Finally, the VTA receives inputs from various brain structures with an important role in the encoding of aversion and stress, such as the central amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and the lateral habenula (LHb), which contacts the VTA both directly and indirectly via the rostromedial tegmental nucleus (RMTg). For clarity, not all connections between nuclei are shown. Instead, the most prominent nuclei presumed to impact on the VTA and to contribute to stress-triggered hedonic feeding are depicted.

(Neuro)peptides affecting VTA-mediated stress feeding

Ghrelin levels are elevated by stress both in humans and in animals, making it another important candidate for mediating stress-induced palatable feeding [107]. A recent study showed that a chronic stress paradigm enhances the rewarding properties and consumption of palatable high-fat food in wild type, but not in GHSR knockout mice. Re-expression of GHSR in TH-containing neurons (among which are VTA dopamine neurons) rescued such effects [108]. Interestingly, GHSR knockout animals also have reduced levels of corticosterone [107]. Therefore, ghrelin may act directly and indirectly on the reward system after stressors. Another potential site of action for ghrelin in stress-induced feeding is the amygdala. Ghrelin infusion in this area leads to increased food intake (although only chow was assessed) and causes a reduction in anxiety levels in food-restricted rats [109].

Orexin is another neuropeptide that plays a role in the general stress response and it elevates corticosterone levels [110]. As described previously, the VTA is a crucial output structure for orexin signaling to produce its effect on palatable food intake [58]. Notably, orexin innervation is also strong in the lateral habenula (LHb) [111], another afferent to the VTA that is activated by unexpected aversive stimuli [16,112]. The LHb provides excitatory input to GABAergic neurons in the RMTg that selectively inhibit VTA dopamine neurons that project to the NAc lateral shell. In addition, LHb neurons provide direct excitatory input to VTA dopamine neurons projecting to the PFC [16]. The LHb, with its direct and indirect projections to the VTA, may therefore be another relevant structure that participates in the encoding of stress feeding.

Cue-induced food seeking

Cues associated with reward can reinstate intake of both drugs of abuse and food [113]. The VTA plays an important role in cue-reward association. It receives glutamatergic inputs that encode information on environmental stimuli. These glutamatergic inputs are potentiated when such stimuli are paired with a reward and thus become 'cues'. After this process, such cues are probably more able to increase dopamine neuron firing via the strengthened inputs to the VTA that occur during their detection. Then they may themselves trigger reward seeking [11,114,115]. Cues associated with rewarding food (e.g., food during a state of food deprivation) later trigger food intake even during satiety, and the PFC, basolateral amygdala (BLA), LH, and hippocampus are crucial in this process [116]. The PFC targets VTA dopamine neurons that project back to the PFC, rather than to the NAc [131]. However, PFC

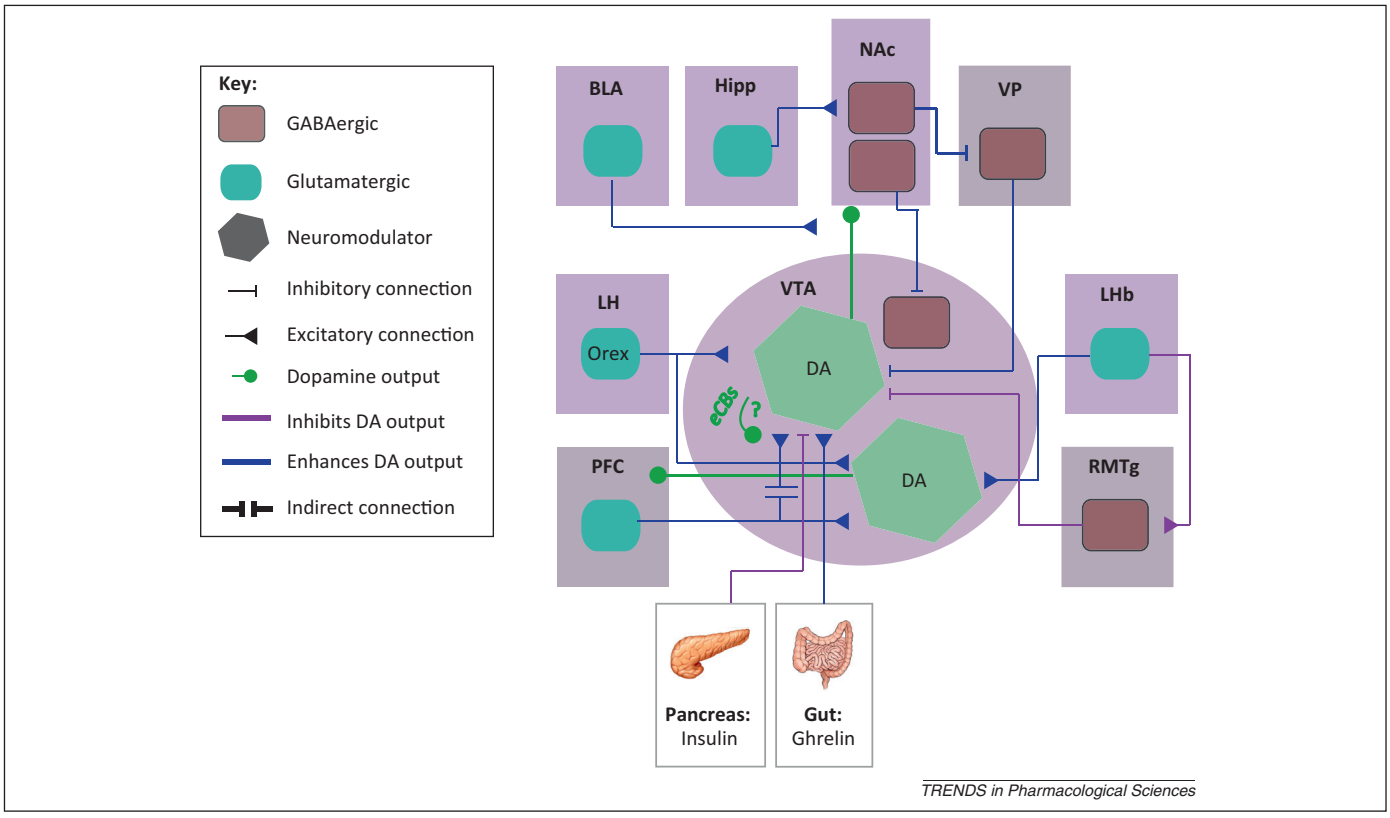

Figure 3. Encoding of cue-induced feeding by the mesolimbic dopamine system. Cues associated with palatable food can gain such significance that they drive food seeking. The ventral tegmental area (VTA) plays a pivotal role in such behavior. Important glutamatergic inputs from the prefrontal cortex (PFC) and lateral hypothalamus (LH) directly impact on the VTA. The basolateral amygdala (BLA) modulates dopamine output in the nucleus accumbens (NAc), probably by affecting VTA terminals. The hippocampus is also important in cue-dependent palatable food seeking, and indirectly acts on the VTA through the NAc and ventral pallidum (VP). The lateral habenula (LHb) also encodes food-related reward cues and may act directly on the VTA or disynaptically through the GABAergic rostromedial tegmental nucleus (RMTg). Again, not all connections between nuclei are depicted. Instead, emphasis is on inputs to the VTA that contribute to cue-triggered hedonic feeding.

stimulation (indirectly through unknown relays) also elevates dopamine signaling in the NAc [132]. The hippocampus mainly affects the VTA indirectly through the ventral striatum [117]. The BLA probably mainly alters dopamine signaling by directly acting at the terminal level in target structures such as the NAc [118]. Notably, a projection from the CeA to the substantia nigra pars compacta (rather than to the VTA) also contributes to cue-directed behavior [119]. The LHb also responds to food-related cues, in a manner typically opposite to that of VTA dopamine neurons. That is, the onset of a reward cue typically inhibits LHb neurons [112]. At the output level of the VTA, dopamine signaling (as well as MOR signaling) in the NAc is important for cue-evoked seeking of palatable food [120]. For the current review we focus on the modulatory factors that act at the level of the VTA to influence food cue-triggered behavior. These key contributors are also depicted in Figure 3.

Input signals affecting VTA-mediated cued feeding

Relatively few neuromodulators acting in the VTA have been conclusively associated with cue-triggered hedonic feeding. One involved player is the endocannabinoid system at CB1Rs in the VTA. Perturbing CB1R signaling in the VTA markedly decreases dopamine signaling in the NAc in response to a predictive food cue. Behaviorally this coincided with decreased palatable food seeking [79]. The relevant synapses modified by cannabinoid signaling in this regard remain unknown, however. Endocannabinoids in the VTA may also contribute to the effects of insulin on cue-induced feeding behavior. Insulin induces a CB1R-dependent long-term depression of glutamatergic input onto VTA dopamine neurons [81]. This physiological effect may underlie the behavioral effect of insulin in the VTA, which is an apparent reduction in the ability to associate cues with food [81]. The origin of the synapses modified by insulin is not known.

The neuromodulator orexin is required for cued hedonic feeding [121]. There is evidence that it may do so by acting in the VTA. Palatable food cues increase markers for neuronal activity in orexin neurons [122,123] and in the VTA [122]. A possible mechanism of action for the effects of orexin on cued feeding may be derived from the literature on drug abuse. Both AMPA receptor and orexin signaling in the VTA are required in order for cues to trigger cocaine seeking [114]. This is due to the ability of orexin to amplify the glutamatergic signal, presumably across a threshold level required to induce cue-induced drug seeking [114]. It is not yet clear where these glutamatergic inputs originate. Potentially they arise from the hypothalamus itself, but orexin has also been shown to potentiate the effect of glutamatergic signals from the PFC to VTA dopamine neurons [124]. In any event, it remains to be verified whether this mechanism for cue-induced drug seeking is indeed also valid for cue-induced hedonic feeding.

There is also a role for ghrelin in cue-induced feeding. In response to food cues, ghrelin levels in fasting humans positively correlate with activity patterns in the hypothalamus and the midbrain [125]. The high ghrelin levels during fasting are also themselves associated with stronger subjective appetite during a food cue responsivity task [125]. In mice, interference with ghrelin signaling prevents food cue-induced feeding in (previously restricted) sated mice [126]. Despite these indications, there is currently no causal evidence for a role of the VTA or dopamine signaling in the effects of ghrelin on cued feeding.

Together, these findings indicate that a neural network comprising cortical regions, limbic systems, the hypothalamus, and the midbrain mediate learned cue-induced responses for palatable food.

Weight loss drugs and the VTA

Many anti-obesity drugs probably also act in the VTA, but it is not known to what extent modulation of VTA activity by these drugs contributes to their weight loss effect. Among these drugs are compounds that mimic activity of GLP-1 (such as liraglutide and exenetide) and leptin (such as metreleptin) signaling, as well as those that promote serotonin signaling, such as, most recently, lorcaserin [127]. A recent development is to combine drugs targeting different transmitter systems such as metreleptin with pramlintide (an amylin analog), and bupropion (a dopamine/noradrenaline reuptake inhibitor) with opioid receptor antagonist naltrexone (this combination is known as Contrave). Which of these targets is most promising depends not only on the efficacy with which weight loss is induced but also on the extent that their manipulation will induce side effects. There is an intrinsic risk with drugs interfering with the midbrain dopamine system, because food reward may be difficult to dissociate from other rewards. Reducing rewarding potential of stimuli in general has the potential risk to induce mood disorders. This seems to have happened with rimonabant (the CB1 inverse agonist), which was withdrawn from the market because of heightened risk for depression and suicide [127]. It may be possible to circumvent this problem with neutral CB1R antagonists, which do not affect the VTA as drastically as inverse agonists [78]. Such findings illustrate that we do not only require a larger understanding of the (peptide) systems involved in hedonic feeding but also a meticulous identification of the correct type of ligand for such a candidate target, so as to not detrimentally perturb these systems instead of rebalancing them.

Concluding remarks

The VTA is a key neural substrate in the pursuit of palatable food, and also when this is triggered by environmental cues or stress. This function is probably all the more used in modern 'obesogenic' environments, where palatable food is widely available, food cues are abundant, and stress is commonplace. In this review many of the key transmitter systems and connections have been highlighted, mainly revolving around the VTA. Although recent insights implicate the VTA in many aspects of food intake, much remains to be determined about how the physiological release of feeding signals in the VTA is integrated, and which downstream targets and circuits are subsequently recruited. Because different subpopulations of dopamine neurons have been identified [4,16], an outstanding question is which dopamine neurons mediate food reward and how signals related to ingestion of food, food cues, and stress reach these neurons. With regard to inputs, the hypothalamus, perhaps in particular the LH, probably represents one of the main crucial inputs to the VTA conveying information about energy balance. Also, the connectivity the VTA has with structures such as the NTS and the PBN, which can integrate information about palatability, is becoming more appreciated. Although beyond the scope of this review, many of the input signals to the VTA that we have discussed here also act on other brain regions to encode important aspects of hedonic feeding. For example, orexin, opioid, and cannabinoid signaling in the NAc shell have all been associated with the direct encoding of hedonic responses to food, a process in which VTA dopamine signaling is not implicated [8]. How all these inputs and connections impact on hedonic feeding is a matter amenable to probing with new tools. In particular, exciting technical developments in this regard come from the fields of optogenetics and designer receptors exclusively activated by designer drugs (DREADD). Optogenetics allows rapid and reversible inhibition or activation of a particular neuronal projection to observe the effects on hedonic feeding. It allows, for example, the investigation of the role of projections from the LH to the VTA in energy balance, or the importance of serotonergic signaling from the raphe nucleus to the VTA for motivation for palatable food. A nice compliment to this comes from DREADD, which works by inserting artificial receptors in cells that are then specifically modulated by the otherwise inert exogenous ligand, clozapine-N-oxide. DREADD offers an easy assessment of more long-term effects of modulating a particular brain region or specific projection, and stimulation or inhibition of DREADDs over days may be needed to induce weight alterations. Tools such as these will greatly help clarify the neural underpinnings of VTA functions such as motivation for palatable food, food cue learning, and (environmentally) triggered hedonic feeding.

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