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Actions of feeding-related peptides on the mesolimbic dopamine system in regulation of natural and drug rewards

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Abstract

The mesolimbic dopamine system is the primary neural circuit mediating motivation, reinforcement, and reward-related behavior. The activity of this system and multiple behaviors controlled by it are affected by changes in feeding and body weight, such as fasting, food restriction, or the development of obesity. Multiple different peptides and hormones that have been implicated in the control of feeding and body weight interact with the mesolimbic dopamine system to regulate many different dopamine-dependent, reward-related behaviors. In this review, we summarize the effects of a selected set of feeding-related peptides and hormones acting within the ventral tegmental area and nucleus accumbens to alter feeding, as well as food, drug, and social reward.

Keywords

Dopamine; VTA; Feeding; Peptide; Reward; Drugs

Introduction

The mesolimbic dopamine (DA) system is the primary neural circuit mediating motivation, reinforcement, and reward-related behavior. This system consists of DA neurons of the ventral tegmental area (VTA) that project to multiple forebrain areas, including the nucleus accumbens (NAcc) and several other limbic structures. At rest, DA neurons fire tonically in a steady, low-frequency mode setting a stable background dopaminergic tone, but when exposed to unexpected salient stimuli of positive or negative valence DA neurons fire in a high-frequency phasic mode which produces high extracellular DA concentrations at efferent targets [1–3]. Activation of the mesolimbic pathway is highly rewarding and reinforcing. For example, rats readily press a lever to electrically stimulate regions along the mesolimbic pathway [4] and some rats even forgo food and starve to continue self-stimulating [5]. This behavior was later shown to be dependent on DA neurotransmission

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[6] and decades of investigation have revealed the breadth of behaviors regulated by the mesolimbic DA system including natural and drug rewards, reinforcement, motivation, and aversion, among others [7–11].

The mesolimbic DA system also plays an important role in the control of feeding and is highly sensitive to changes in feeding status and body weight. For example, fasting and prolonged food restriction increase DA system function and increase the reinforcing qualities of, and motivation to obtain, nearly all rewarding substances [12]. In addition, increases in body weight, such as those seen in obesity, alter DA circuit function and multiple DA-dependent behaviors [13–16]. Some of these effects may be due to the actions of feeding-related neuropeptides and hormones on the mesolimbic DA system. Multiple central and peripheral peptides and hormones that are intricately involved in the control of feeding and body weight to either promote (orexigenic) or inhibit feeding (anorexigenic) have been shown to interact with the mesolimbic DA system to regulate multiple behaviors. This includes feeding, the motivational and rewarding aspects of food, as well as drug-reward associated and social behaviors. In this review, we summarize the effects of a selected set of feeding-related peptides and hormones acting within the VTA and NAcc to alter feeding as well as food, drug, and social reward Table 1. provides an overview of the studies showing the effects of these peptides and hormones on food, alcohol, drug, and social behaviors, which are described in detail in the following sections.

Melanocortins

The melanocortin peptides, α-melanocyte-stimulating hormone (α-MSH) and agouti-related protein (AgRP), are well known for their role in the regulation of feeding but they also participate in the control of many other behaviors and physiological functions [17–19]. α-MSH is produced by proteolytic cleavage of proopiomelanocortin (POMC) propeptide produced by POMC neurons of the arcuate nucleus of the hypothalamus (Arc) as well as the commissural nucleus of the solitary tract (NTS). In contrast, Arc AgRP neurons are the sole site of AgRP production and release [17,18,20]. In the central nervous system, melanocortin peptides bind to two receptors, the melanocortin-3 and −4 receptors (MC3R and MC4R) with α-MSH acting as an agonist and AgRP acting as is an inverse agonist/competitive antagonist. AgRP neurons also release neuropeptide Y (NPY) which binds to a family of multiple NPY receptors (NPYR) and is discussed in the next section. The initial evidence showing that melanocortins can interact with mesolimbic DA circuits was the demonstration that either intracerebroventricular (ICV) or direct intra-VTA injection of α-MSH stimulated DA release in efferent projection areas such as the NAcc and the prefrontal cortex, and stimulated grooming and rearing behavior [21–24]. Analysis of the anatomy of the melanocortin circuits and their receptors also provided evidence for their interactions with the mesolimbic DA system. MC3Rs and MC4Rs are expressed in both VTA and NAcc [25–28]. Moreover, VTA is one of the regions with the highest expression of MC3Rs, which are expressed in DA and non-DA neurons [27–29]. Both POMC and AgRP neurons project to the VTA [30–32] and prolyl carboxypeptidase, an enzyme responsible for inactivation of α-MSH, is expressed in the VTA [33] suggesting that mechanisms regulating α-MSH dynamics are present within this region. Surprisingly, with the use of monosynaptic cell-type-specific rabies virus, we recently showed a low degree of synaptic connectivity

between Arc neurons, including AgRP/NPY and POMC populations, and multiple VTA neuron subtypes [31]. These results were further validated by another group that showed low amount of AgRP/NPY synaptic terminals in the vicinity of VTA DA neurons compared to the robust labeling in the paraventricular nucleus (PVN) [34]. The same group also reported a lack of inhibitory postsynaptic currents produced by ChR2-mediated activation of AgRP/NPY terminals in the VTA and unchanged basal activity of VTA DAT neurons in response to chemogenetic activation of Arc AgRP/NPY neurons [34]. This lack of synaptic connectivity, coupled with the robust labeling of POMC and AgRP neurons by generic retrograde tracers injected into the VTA [31,35] and the previously reported presence of AgRP terminals in close proximity to putative dopamine neurons of the VTA [30], suggest that Arc feeding peptides act on the VTA circuitry via short distance diffusion. It is currently not known whether α-MSH and AgRP are released from axons of neurons traveling through the VTA on their way to more caudal regions, however. This possibility is less likely than extra-synaptic transmission from direct AgRP and POMC neuronal projections to the VTA as AgRP neurons have been reported to show little collateralization [36]. In contrast to our findings, another group has reported Arc POMC+ synaptic terminals and boutons in the proximity of VTA DA and non-DA neurons [32] and showed that Arc POMC neurons inhibit VTA DA neurons via direct and indirect mechanisms [37]. These findings conflict with the data showing that α-MSH increased extracellular DA in NAcc and increased DA-dependent behaviors however [21,22], as well as the data from our laboratory showing that α-MSH increased the firing rate of MC3R-expressing VTA neurons in acute slices [38]. In this section, we will focus on the effects of melanocortin action within mesolimbic circuits in the regulation of feeding and drug reward whereas the effects on alcohol intake and reward have been discussed in detail in a recent review [39].

Food and food reward:

Melanocortin peptides are well known for their regulation of feeding. Stimulation of POMC neurons and injection of melanocortin receptor (MCR) agonists have been widely shown to decrease food intake and increase energy expenditure and metabolism [40–42], whereas central administration or overexpression of AgRP and activation of AgRP neurons promotes feeding and weight gain [40,43–46]. Some of these effects appear to be mediated through actions in the mesolimbic DA system. For example, our laboratory has shown that administration of non-specific MCR agonists into the VTA decreased the intake of both standard chow and palatable sucrose solutions, and decreased sucrose self-administration, whereas injection of MCR antagonists into the VTA increased chow intake, body weight, and sucrose self-administration [47–49]. Contrary to our findings with the non-selective MCR agonist MTII, another group showed that intra-VTA infusion with D-trp^8-γMSH, an MC3R-selective agonist, increased sucrose self-administration but not free feeding on sucrose, illustrating the difficulty in resolving the exact role of MCRs in the VTA [50]. Injection of α-MSH and AgRP into the NAcc shell also produced a decrease and an increase in motivation for sucrose, respectively [51]. Although MCR knockout results in increased weight and fat mass, diabetes, and altered activity [52–55], suggesting that both receptor subtypes are important for energy homeostasis, it isn't clear whether the MC3R or MC4R a larger role in the effects of α-MSH and AgRP within the mesolimbic DA system circuitry. Global deletion of MC3R altered food self-administration under fixed ratio-1 and

progressive ratio conditions in food-restricted mice but not under normal *ad libitum* feeding, and re-expression of MC3Rs exclusively in DA neurons reversed the changes in progressive but not fixed ratio, responding [56]. MC3R knockout also sex-dependently altered sucrose preference and DA turnover [28]. Taken together, these data suggest that MC3Rs may be the point of interaction between the homeostatic melanocortin peptides and the mesolimbic circuitry, likely through their interactions in the VTA because of the abundance of MC3R in that region [27]. Furthermore, our laboratory recently showed that MC3R-expressing neurons of the VTA control feeding in an activity- and sex-dependent manner such that acute activation of these neurons decreased feeding, but only in females, and acute inhibition of them decreased feeding, but only in males [29] further supporting the contextual and sex-dependent roles of MC3R-mediated signaling in the VTA. There have also been several reports of VTA MC4R-dependent regulation of DA dynamics and feeding [57],58. However, these studies used MC4R-selective ligands that still show significant affinity for MC3R [59]. Because of this, and the abundance of MC3R receptors and low amount of MC4R receptors in the VTA [28], studies utilizing MC4R-selective ligands should be interpreted cautiously. In contrast to the VTA, the NAcc is enriched in MC4R and lacks MC3R [27,60]. Similar to what was observed in the VTA, NAcc injection of MC4-R agonists decreased and antagonists increased feeding [57]. Future studies enabled by the use of recently developed genetic tools and new ligands showing higher specificity for MC3Rs vs MC4Rs will aid in furthering our understanding of mechanisms associated with melanocortin action in the mesolimbic DA system.

Effects on drugs of abuse:

Activation of MCRs appears to have a potentiating effect on drug reward and reinforcement for multiple drugs. For example, ICV injection of non-specific MCR agonists enhanced the reward-potentiating effects of amphetamine on lateral hypothalamus (LH) self-stimulation [61]. Likewise, ICV administration of α-MSH or an MC4R agonist potentiated nicotine reward in an intracranial self-stimulation (ICSS) paradigm in an ovariectomized rat menopausal female model, whereas MC4R antagonists suppressed the ICSS promoting effects of nicotine [62]. MC4R null mice show blunted cocaine locomotor sensitization which is normalized by restoration of MC4R expression in Dopamine receptor D1 (D1R)-expressing neurons [63]. Furthermore, NAcc injection of MCR antagonists blocked multiple aspects of cocaine reward including reinforcing, motivational and sensitizing effects of the drug [60] illustrating the direct involvement of NAcc MCRs in the effects on cocaine reward. The roles of the melanocortin peptides or their receptors within the VTA in the regulation of drug reward have not been investigated to date, however.

NPY

NPY is a potent orexigenic peptide that is expressed widely throughout the CNS including the Arc and structures of the mesolimbic system. For example, NPY is produced locally by NAcc neurons and the NAcc also receives input from Arc NPY neurons [64,65]. As discussed in the previous section, Arc NPY neurons also project to the VTA, and the area receives additional NPY input from the ventrolateral medulla of the brainstem [30,31,66]. Unlike the NAcc, the VTA lacks NPY-expressing cell bodies, and blockade of neuronal

peptide transport by colchicine eliminated VTA NPY signal [66] suggesting that in the VTA, NPY immunoreactive fibers are exclusively external. NPY mediates its effects through five known receptors, NPY1R-NPY6R [67] although NPY6R is not expressed in the rat brain. NPY1R and NPY5R are expressed in the VTA and NAcc and NPY5R binding has been confirmed in the latter [68–71]. In *ex vivo* experiments, NPY has been shown to affect VTA DA neuron activity via multiple pre and postsynaptic mechanisms including direct inhibition of DA neurons, and a decrease in presynaptic glutamatergic and GABAergic transmission [68,72]. The net effect of NPY action in the VTA is currently unknown, however. In the NAcc, NPY infusions increased DA concentrations [70,73] suggestive of NPY-mediated stimulation of DA release.

Food and food reward:

NPY is an important regulator of feeding as shown by the robust increase in feeding produced by central administration of the peptide [74,75] or optogenetic stimulation of Arc NPY neurons [40]. Furthermore, ablation of NPY neurons has been shown to reduce feeding and body weight [76,77]. Additionally, central administration of NPY increased motivation to obtain food pellets, indicating that the mesolimbic system may be one of the targets of NPY [78]. In fact, injection of NPY into the VTA or the NAcc increased motivation to respond for sucrose [79]. The mesolimbic system-mediated effects of NPY in the regulation of feeding appear to be macronutrient selective. For example, intra-VTA or -NAcc injection of NPY did not affect intake of sucrose or regular chow [65,79,80] but increased intake of fat when administered into the NAcc via NPY1R -dependent mechanism [65].

Alcohol intake and reward:

Central administration of NPY or NPY1R agonists have been shown to decrease ethanol intake in genetically vulnerable rodent models [81–83]. Furthermore, NPY also contributes to the regulation of alcohol-directed reinstatement and relapse behaviors. For example, ICV infusion of NPY has been shown to block stress-induced reinstatement of ethanol seeking [84] and, when administered during the withdrawal period, reduced increases in ethanol self-administration in subsequent withdrawal trials [85]. Within the mesolimbic circuitry, activation of NAcc NPY2R reduced expression of ethanol-induced behavioral sensitization [86]. On the other hand, intra-NAcc shell administration of NPY or NPY1R agonists dose-dependently increased ethanol self-administration directly into the posterior VTA, whereas NPY1R antagonist produced the opposite effect [87] potentially suggestive of NPY-mediated enhancement of DA release in the NAcc shell. Little is known about the role of VTA-targeted NPY action in the regulation of ethanol-directed behaviors, however.

Effects on drugs of abuse:

Unlike the mechanisms involved in the regulation of ethanol-directed behaviors which appear to be mediated through NPY1R and NPY2R but not NPY5R [88–90], NPY5R seems to play an important role in NPY effects on drugs of abuse. For example, global knockout of NPY5R attenuated cocaine self-administration and cocaine-induced hyperlocomotion [91]. Furthermore, ICV administration of NPY during abstinence attenuated morphine withdrawal symptoms in an effect mediated via receptors with a NPY5R-like pharmacological profile [92]. NPY administration into NAcc shell also prolonged the extinction period following

chronic morphine exposure whereas blockade of NPY5R receptor signaling reduced it [93]. The same group also showed that chronic morphine exposure reversibly decreases NPY expression in the NAcc shell [93]. Despite this evidence implicating NPY5R s, in the NAcc shell, NPY also acts via NPY1R to regulate drug of abuse-related reward behaviors. For example, injections of NPY or NPY1R agonists potentiated and a NPY1R antagonist attenuated the rewarding effect of morphine as measured by ICSS of medial forebrain bundle [94]. The intra-VTA effects of NPY in the regulation of drug-directed behaviors are currently not known and require attention.

Corticotropin-releasing factor

Corticotropin-releasing factor (CRF) is a key neuropeptide in the stress response. CRF is produced by the neurons of multiple hypothalamic and limbic regions including PVN, bed nucleus of the stria terminal is (BNST), and the central amygdala and CRF-containing fibers populate the NAcc core, NAcc medial shell, and the VTA [95–97]. Additionally, a subset of VTA DA neurons also co-express CRF [98]. Within the VTA, DA neurons receive mostly asymmetric (excitatory) input from CRF+ terminals, whereas non-DA neurons receive both symmetric (inhibitory) and asymmetric inputs [99,100]. This anatomical diversity is further supported by electrophysiological studies which showed both inhibitory [101] and excitatory [102,103] effects of CRF on the VTA DA neurons. CRF binds to two receptors, CRFR1 and CRFR2, although the peptide has higher affinity for the former [104]. Both of these receptors are expressed throughout the brain, including the mesolimbic structures [97,105]. In the VTA, CRFR1 is located both presynaptically and postsynaptically [106] and colocalizes with TH and D1R [107]. The expression of CRFR2 in VTA has been difficult to resolve [108] but, as discussed below, has been implicated in behavior. In NAcc neurons, CRFR1s do not colocalize with tyrosine hydroxylase (TH) or D1R [107], whereas dopaminergic terminals populating NAcc express both receptor subtypes suggestive of DA-release regulatory function of CRF in that area [95].. In support of this, direct administration of CRF into NAcc has been shown to elevate DA, but only in animals that were not stressed [95]. The urocortin peptides are CRF analogs that act via CRFR1 and CRFR2. Although the urocortins have been implicated in both feeding and social behavior, their actions directly within the mesolimbic system have not been highly studied, so they will not be discussed here.

Food and food reward:

Stress-facilitated eating, especially of highly palatable and calorically dense foods, is a well-known phenomenon. Yet, little attention has been focused on the interaction between CRF and the mesolimbic system in the regulation of feeding. One study showed that CRF acts in the VTA to reduce motivation for food reward [109]. Conversely, through its action in the NAcc, CRF has been shown to amplify incentive salience of sucrose reward. For example, CRF injected into NAcc shell enhanced the ability of Pavlovian reward cues to trigger instrumental performance for sucrose reward [110]. It is possible that CRF may contribute to the changes in mesolimbic DA system function that occur in response to fasting and food restriction, both of which elevate CRF levels, but this has not been directly

tested to date. Overall, more studies are necessary to understand the role of CRF and stress in the regulation of feeding and food reward.

Alcohol intake and reward:

As postulated by the tension reduction hypothesis, stress augments anxiety, and alcohol is then consumed to reduce this anxiety [111]. This hypothesis establishes a clear link between stress and alcohol consumption but the real picture and the mechanisms involved in alcohol dependence are much more complicated as discussed in another review [112]. The physiological effects of the hormonal mediator of stress, CRF, have been strongly linked to alcohol-taking behaviors. For example, CRFR1 antagonists have been shown to decrease alcohol drinking in binge and intermittent access paradigms [113–115], to decrease ethanol self-administration in dependent animals [116], to decrease anxiety-like behavior during ethanol withdrawal [116], and to decrease stress-induced reinstatement of ethanol seeking [117]. The VTA has been established to be an important site of CRF action in the regulation of binge-like ethanol consumption as shown by a decrease in binge-like drinking in response to intra-VTA CRFR1 antagonist administration [118,119]. Interestingly, VTA activation of CRFR2 also decreased binge-like drinking and it has been suggested that the reduction in binge-like ethanol intake produced by CRFR1 antagonism requires intact CRFR2 signaling [118]. Furthermore, BNST CRF input to the VTA, rather than local VTA CRF-producing neurons, has been identified as the driver of binge-like ethanol drinking [118]. VTA CRFR1 antagonism was also shown to reduce alcohol consumption in an intermittent access two-bottle choice paradigm regardless of intrinsic alcohol preference of the animals [115]. VTA CRF signaling via CRFR1 was also shown to be important for social defeat stress-induced escalation of ethanol drinking while signaling via CRFR2 produced non-alcohol specific reductions in intake [120]. Thus, CRF clearly interacts with the mesolimbic DA system to regulate ethanol responses.

Effects on drugs of abuse:

The existence of a positive correlation between stress and drug use is well known. For example, CRF administration facilitated reinstatement of cocaine seeking following extinction [121–123]. CRFR1 has also been consistently shown to be involved in stress-mediated cocaine behaviors including reinforcement and relapse. For example, peripherally administered CRFR1 antagonists reduced cocaine self-administration in multiple paradigms [124,125], blocked stress-induced increase in cocaine conditioned place preference (CPP) [126], attenuated stress-induced reinstatement of cocaine CPP [127,128], and stress-induced reinstatement of cocaine seeking [129,130]. The VTA is one of the key neural substrates of CRF-mediated effects on cocaine behaviors. For example, VTA infusion of CRF reinstated lever pressing for cocaine in cocaine-exposed animals [100,130]. Furthermore, stress-induced reinstatement of cocaine seeking has been linked to the physiological action of CRF in the VTA as shown by blockade of foot shock-induced reinstatement by intra-VTA infusion of general CRF antagonist [100]. The mechanism of CRF action in the VTA is complex and not well understood, however. Both CRFR1 [127,129,131,132] and CRFR2 [100,130] have been causally, and in some studies mutually exclusively, implicated in the VTA-directed CRF effects. However, another study showed that the same behavior can be regulated by both receptors as antagonists for either CRF receptor subtype administered

into the VTA during social defeat stress prevented dopaminergic cross-sensitizations and escalated cocaine self-administration in a 24-hour binge protocol [133]. Interestingly, short hairpin RNA-mediated knockdown of VTA CRFR1 reduced cue-induced cocaine seeking but not cue-induced sucrose seeking [132] suggesting differential regulation of drug and natural rewards by CRF.

There is no surprise that stress, and by extension CRF, also participate in the regulation of nicotine-directed behaviors. Blockade of CRF action [134], and specifically the effects mediated by CRFR1 [135], decreased stress-induced reinstatement of nicotine seeking. Additionally, CRF is involved in nicotine withdrawal effects as shown by a decrease in measures of precipitated nicotine withdrawal in response to CRFR1 antagonist treatment [135]. VTA appears to be one of the CRF targets in the modulation of withdrawal-associated behaviors as blockade of VTA CRFR1 prevented anxiety-like behavior during nicotine withdrawal [98]. Overexpression of CRF in NAcc increased operant responding to nicotine in sexually dimorphic manner with females exhibiting higher levels of responding. Furthermore, this effect was shown to be dependent on ovarian hormones as nicotine self-administration was increased to a larger extent in intact compared to ovariectomized females [136]. Interestingly, NAcc CRF overexpression also increased food intake to a larger extent in females than males but this effect was not dependent on ovarian hormones [136].

Melanin-concentrating hormone

Melanin-concentrating hormone (MCH) is a cyclic peptide predominately synthesized by neurons of the LH and zona incerta from a precursor encoded by *Pmch* gene [137]. LH MCH neurons send widespread projections throughout the brain including dense innervation of the VTA and NAcc [137,138]. MCH binds to two receptors, MCHR1 and MCHR2, but all preclinical research on MCH has focused on the MCHR1-mediated actions of the peptide as MCHR2 is not expressed in rodents [139]. MCHR1 is highly enriched in NAcc shell [140–142] and is coexpressed with DA receptors [143,144]. Low to moderate levels of MCHR1 mRNA have been previously detected in the VTA [140–142] but no detectable VTA MCHR1 expression was found in BAC knock-in mice [145]. Optogenetic stimulation of MCH neurons has been shown to increase NAcc DA [146], yet, in VTA slices, MCH application did not affect firing rate [147] and intra-VTA MCH injections failed to produce changes in DA-dependent behaviors [24]. Together with anatomical data, these results, as well as those discussed below, suggest that VTA is a minor target of MCH whereas NAcc is the primary mesolimbic substrate of MCH action in the regulation of feeding and reward behaviors. The role of MCH in the regulation of feeding and food reward has received the most attention whereas much less is known about the effect of this peptide on the behaviors associated with intake of alcohol and drugs of abuse. This review will discuss food and food reward-related findings whereas the role of MCH in drug abuse disorders has been discussed in greater detail in a recent review [148].

Food and food reward:

The role of MCH as a critical regulator of feeding is supported by both pharmacological and genetic data. For example, loss of *Pmch* resulted in hypophagia and a lean phenotype

[149] whereas overexpression of MCH caused hyperphagia and excess weight gain [150]. Similarly, MCH administered centrally increased feeding and body weight [151,152] whereas systemic treatment with MCHR1 antagonist reduced food intake and body weight in animals with diet-induced obesity [153,154]. In the mesolimbic circuit, MCH exerts its feeding effects by acting primarily in the NAcc shell as shown by an orexigenic response to intra-NAcc shell MCH injection and a reduction of feeding produced by MCHR1 antagonist injected into this area [155]. Additionally, MCH administration to the NAcc shell of *Pmch* null mice restored feeding to wild-type levels [156]. Recently, Terrill et al. showed that MCH action in the NAcc in the regulation of feeding is sexually dimorphic as NAcc shell treatment with MCH or chemogenetic activation of LH-MCH projections to the region promoted feeding, but only in males. This effect was shown to be estrogen-sensitive as ovariectomy restored the ability of MCH to promote feeding in females [157].

MCH also regulates rewarding and motivational aspects of feeding. For example, MCHR1 antagonists reduced consumption of palatable sweetened condensed milk in sated rats [154]. The NAcc appears to be involved in this effect as shown by MCH-induced increase in sucrose intake when the peptide is administered directly into this region [157]. Peripheral administration of MCHR-1 antagonists or loss of *Pmch* reduced food self-administration in food-restricted animals as well as high-fat food-reinforced operant responding and sucrose but not saccharin self-administration [156,158,159] suggesting that MCH may be important for the motivational aspects of feeding, especially of nutritive substances. Surprisingly, MCH administration into NAcc shell or chemogenetic activation of NAcc-projecting MCH neurons did not affect operant responding for sucrose, however [157]. In fact, MCH appears to play a complex role in the regulation of intake of sweet substances such that it conveys rewarding signals from the caloric content rather than the taste of the ingested sugars [146,158]. The mechanism or the neural substrates responsible for this effect are currently not known, however. Additionally, conflicting data exist regarding MCH's effects on reinstatement of food seeking. For example, MCHR1 antagonists reduced MCH-induced reinstatement of food seeking but had no effect on high-fat food, cue, or stress-primed reinstatement [159]. Conversely, cue-induced reinstatement of sucrose seeking was decreased by MCHR1 antagonism [158]. The mechanisms underlying these differences need to be investigated in future experiments.

Orexin

The two orexin (OX) peptides, orexin A and orexin B (OX-A, OX-B), also known as hypocretins, are neuropeptides alternatively spliced from a common precursor and are produced by the neurons of the lateral, dorsomedial, and perifornical areas of the hypothalamus. Interestingly, OX neurons show a similar distribution to MCH neurons and are interspersed with them. The OX peptides bind to two distinct receptors, orexin 1 (OX1R) and orexin 2 (OX2R), to regulate many behaviors including arousal, feeding, and appetitive behaviors [160,161]. Like MCH neurons, OX neurons project widely throughout the brain and OX receptors are expressed in many brain regions including the components of the mesolimbic system [162,163]. Both VTA and NAcc receive input from OX-A- and OX-B-containing neurons of LH and OX-containing terminals are found in close opposition to VTA DA neurons [164]. Moreover, both OXRs are expressed in the VTA

and NAcc [162,165,166]. A large body of literature supports the idea that OX regulates DA neurotransmission and DA-dependent behaviors. For example, ICV OX produced classic DA-dependent behaviors such as hyperlocomotion and stereotypy that were blocked by a DA receptor antagonist [167]. Furthermore, OX has been shown to directly activate VTA DA neurons, including those projecting to NAcc shell, and to produce increased DA outflow in the NAcc [147,167–171].

Food and food reward:

Peripheral or ICV injections of OX peptides increased food intake [161,172–178] and central administration of anti-OX antibody or an OX1R-selective antagonist reduced food intake [173,179]. Furthermore, blockage of OX1R also reduced intake of highly palatable food and binge-like consumption of sucrose [180–183]. OX1R-mediated signaling also appears to play an important role in the regulation of food reinforcement and motivation as was illustrated by decreased performance under variable and progressive ratio of reinforcement produced by peripheral OX1R blockade and LH OX knockdown [184]. Moreover, ICV OX-A has also been shown to reinstate previously extinguished food-seeking behavior [185].

Unlike the peripheral effects, intra-VTA administration of OX did not stimulate feeding on chow diet [178]. Conversely, OX-A administered into the VTA increased the intake of high-fat diet (HFD) and sucrose solution in *ad-libitum* fed rats, and this increase in sucrose feeding was mediated by OX1R as the receptor blockade attenuated sucrose intake [186]. Furthermore, in a hedonic model of feeding in which food-restricted animals are exposed to HFD following chow refeeding, OX-A acted in the VTA to increase intake of both chow and HFD [186]. Together, these experiments suggest that OX acts in the VTA to promote palatable food intake rather than to modulate normal baseline chow feeding. These results are also in line with the idea that VTA OX may play a role in feeding under high-motivation conditions as VTA blockade of OX-1R blunted orexigenic effects of ICV ghrelin [187]. Furthermore, intra-VTA OX-A attenuated intragastric nutrient-induced hypophagia [186] suggesting that OX action in the VTA counteracts postingestive negative feedback.

In the NAcc, infusion of OX-A into the shell of the nucleus increased feeding and locomotor activity, and the effect on feeding but not locomotor activity was attenuated by pretreatment with OX1R antagonist [188]. These results suggest that in the NAcc feeding and locomotion may be modulated by different molecular mechanisms. Injection of OX-A into the previously identified “hedonic hotspot” within the rostral region of the NAcc medial shell, a region that was previously shown to be the target of opioid enhancement of sucrose liking as measured by taste reactivity [189], also increased the hedonic impact of sucrose taste. Meanwhile, the intake of palatable food was enhanced by OX-A injections throughout different regions of NAcc shell [190]. Not much is known about the specific interactions of VTA/NAcc with OX in the regulation of food-motivated behavior, however. Future experiments are necessary to fill this knowledge gap.

Alcohol intake and reward:

Multiple excellent reviews have focused on discussing the role of OX in the regulation of alcohol intake and reward (please refer to [191,192]). In this review, we will specifically focus on literature investigating the direct action of OX on the mesolimbic structures. Like the effects on sucrose and saccharin, peripheral administration of OXR antagonists disrupts binge-like consumption of ethanol [193,194]. Within the VTA, selective blockade of OX1R but not OX2R significantly blunted binge-like ethanol intake [195] suggesting that VTA is one of the neural substrates of OX action in the regulation of ethanol binge drinking. OX action in the VTA is also involved in the regulation of operant behavior directed towards alcohol as shown by the attenuated alcohol self-administration following intra-VTA treatment with dual OX1R/OX2R antagonist [196]. OX has been strongly implicated in regulation of alcohol-directed behaviors in high alcohol consumers and the mesolimbic circuitry appears to be involved in this. For example, systemically administered OX1R antagonist decreased alcohol consumption, preference, self-administration, and reinstatement selectively in high ethanol preferring/responding rats [197]. Similarly, blockade of NAcc shell OX1Rs decreased alcohol intake in a 2 bottle choice drinking in the dark and intermittent access paradigms [198,199] and this effect was only observed in excessive drinkers with no effect in moderate drinkers [199].

Effects on drugs of abuse:

The effects of OX action on the expression of behaviors moderated by the drugs of abuse and involved in addiction have received the most attention and have been reviewed in detail previously [200–202]. OX action in the VTA is strongly implemented in the regulation of reinforcement properties of cocaine. For example, intra-VTA infusion of OX-A promoted cocaine self-administration under multiple models of reinforcement schedule [203] and both systemic and intra-VTA administration of OX1R antagonist reduced cocaine self-administration [204,205]. OX is also involved in the development and expression of drug-induced locomotor sensitization but the effects differ for different drugs. Similar to its systemic effect, OX1R antagonist delivered into the VTA prevented acquisition but not the expression of locomotor sensitization to cocaine [206]. However, systemically administered OX1R or dual OX1R/ OX2R antagonist blocked the expression of sensitization and blocked the expression of amphetamine-induced markers of synaptic plasticity in the VTA [207,208]. OX also acts on different modalities of the mesolimbic system to regulate drug seeking. Intra-VTA administration of OX peptides reinstated previously extinguished morphine and cocaine preference [209,210] and blockade of OX1R in the VTA attenuated cue-induced cocaine reinstatement [211] but not stress-induced cocaine reinstatement [210]. Conversely, blockade of NAcc shell OX1R or OX2R attenuated stress-induced morphine reinstatement but not morphine primed reinstatement [212]. Taken together, it appears that OX acts on the VTA neurons to regulate cue-induced drug-seeking behavior and it acts in the NAcc shell to mediate stress-induced drug-seeking responses.

Oxytocin

Oxytocin (OT) is a neuropeptide produced by the PVN and supraoptic nucleus neurons that is well known for its role in bonding and social behavior but this peptide is also

an important regulator of feeding and reward. This review will focus on the actions of OT in the mesolimbic DA system whereas its roles in the regulation of other behaviors are discussed in greater detail in the following reviews [213,214]. OT influences behavior primarily through its action on the oxytocin receptor (OTR), although it can also bind to vasopressin 1A receptors with lower affinity [215]. Both the VTA and NAcc express OTRs [216–218] and receive input from OT-expressing PVH neurons [217,219–222] although OT can also signal via volume transmission [223]. OT has been shown to, directly and indirectly, impact VTA neuron activity [219,224,225], DA release [226,227], and to facilitate DA-dependent behaviors [228,229]. Interestingly, almost 50% of OTR-expressing neurons co-express vGlut, whereas only 10% colocalize with TH [217] suggesting that glutamatergic signaling by VTA neurons plays an important role in OT-mediated effects.

Food and food reward:

Peripheral or central administration of OT decreased feeding in *ad libitum* and food-deprived conditions and treatment with OTR antagonist increased feeding [230–234]. Likewise, peripheral OT injection attenuated sucrose intake, and treatment with an OTR antagonist increased sucrose consumption [235,236]. OT has also been shown to participate in the regulation of fat intake [229,237–239]. However, systemically administered OT antagonist shifted the preference toward sucrose consumption without affecting total energy intake when animals were given a choice between fat and sucrose diets [235] suggesting that OT preferentially regulates carbohydrate intake. This is consistent with observations from OT null mice which overconsume palatable sucrose solution but not fat emulsion solution [240]. In addition to intake, OT also attenuated food reward-related behaviors such as sucrose self-administration and sucrose seeking [229,241–243], and disrupted the expression but not acquisition of sucrose place preference [244].

Intra-VTA injection of OT has been reported to reduce chow intake when measured at a short-term time point [234] without an overall effect on overnight chow consumption [229]. OT delivery to the VTA also decreased the intake of sucrose but not water in deprived animals [229] suggesting that OT action in the VTA is directed towards sucrose consumption rather than general modulation of reward. The same research group also showed that endogenous OT signaling in the VTA is physiologically relevant to attenuation of sucrose intake as shown by intra-VTA OTR antagonist-mediated increase in sucrose intake [229]. Furthermore, OT delivered to the VTA has been shown to reduce food motivation and food seeking [234] supporting the idea that OT-mediated reduction in food reward contributes to the central anorexigenic effect of this peptide. OT signaling in the NAcc core but not shell also decreased reward-related feeding behaviors such as chow intake in deprived conditions, and the consumption of palatable nutritive and non-nutritive sweet solutions [245]. In obese humans, OT administration has been shown to reduce functional connectivity between the VTA and brain areas involved in the regulation of food-motivated behaviors in response to viewing high-calorie food imagery [246] potentially providing a translational mechanistic insight into OT-mediated anorexigenic effects. In fact, an OT derivative is currently being reviewed by the FDA for the treatment of hyperphagia in individuals with Prader-Willi Syndrome [247], a genetic disorder characterized by insatiable hunger and life-threatening obesity.

Alcohol intake and reward:

In human trials, intranasal OT has been shown to block alcohol withdrawal in dependent individuals [248] illustrating the clinical utility of OT in treatment of alcohol dependency. Animal work conducted by several groups also supports the role of OT in the regulation of alcohol consumption and reward but there is a large knowledge gap regarding the mechanisms or the neural substrates of OT's action in the regulation of these behaviors. Multiple studies had shown that peripheral and/or central treatment with OT reduced alcohol consumption [249,250], including binge-like intake of alcohol [251], reduced operant responding for ethanol [251,252], and decreased stress- and cue-induced reinstatement of alcohol seeking [253,254], although the latter was only decreased in alcohol-dependent animals. The mesolimbic system is known for regulating all of the afore-mentioned behaviors but very little is known about the action of OT on the mesolimbic circuits in regulation of alcohol-related behaviors. It has been previously shown that ICV OT blocked ethanol-induced DA release in NAcc [252] and overexpression of OTR in NAcc reduced ethanol preference, ethanol intake, and reinstatement of ethanol conditioned place preference [255,256]. The effects of OT in the VTA in the regulation of alcohol-related behaviors remain largely unknown, however.

Effects on drugs of abuse:

The systemic and central effects of OT in the regulation of behaviors associated with drug reward are well documented for multiple substances including cocaine, opioids, methamphetamine (METH), and nicotine, and have been discussed in detail in a recent review [257]. Although the mesolimbic system is known for its involvement in the regulation of addictive behaviors, there is a knowledge gap in understanding how OT interacts with the mesolimbic structures to regulate drug reward. Several studies have examined the actions of OT in the NAcc in regulation of drug-associated behaviors. For example, intra-NAcc OT has been shown to attenuate METH-induced CPP [258], drug seeking and demand [259], as well as METH-primed reinstatement [260]. This latter effect was OTR-independent, however, as shown by the lack of reversal in response to co-administration of OTR antagonist [260]. Similarly, direct infusion of OT into NAcc inhibited cocaine-seeking behavior [261,262] and heroin self-administration [261]. The role of VTA action of OT in modulation of behaviors directed towards drugs of abuse remains largely unexplored and requires attention, however.

Effects on social reward:

OT is well known for its role in social interactions, including social reward, and the mesolimbic system is a critical target of OT's action in regulation of these behaviors. Intra-VTA administration of OT or OTR agonist showed that activation of VTA OTRs is necessary for the expression of rewarding properties of social interactions [263]. Furthermore, optogenetic stimulation of PVN OT neuron axons in the VTA promoted sociability whereas silencing of PVN OT neuron projections in the VTA reduced social interactions [264] suggesting that endogenous OT signaling in the VTA is necessary for social reward. Interestingly, when the animals were tested in a novel Operant Social Preference task which, unlike CPP, does not contain a memory confound [265], intra-VTA OT decreased

the frequency of seeking social interaction and OTR antagonist increased the frequency of entering social interaction chambers [266] showing that, in the VTA, OT plays a complex role in the regulation of reinforcing properties of social interaction. OT action within the NAcc has also been shown to be important for social reward. For example, intra-NAcc injection of OTR antagonist prevented social CPP [267]. This effect was mediated by presynaptic action of OT as OTR deletion from the cells of NAcc did not affect social CPP whereas deletion of presynaptic OTRs, specifically those projecting from dorsal raphe, completely blocked CPP [267].

Amylin

Amylin (Amy) is an anorexigenic peptide co-secreted with insulin by pancreatic β-cells. This peptide signals through the Amy receptor (AmyR) which is a dimerized complex of a calcitonin receptor (CTR) and a receptor activity-modifying protein. Amy inhibits pancreatic glucagon release, delays gastric emptying, reduces gastric acid production, and acts as a satiety agent (the diverse physiological effects of Amy are more thoroughly discussed in a previous review [268]). In 2005, the Amy analog pramlintide acetate received FDA approval for treatment of type 1 and type 2 diabetes [269,270] and, in addition to being a potent glycemic regulator [271], Amy has been shown to reduce food intake in humans [272–274]. The area postrema and NTS have been regarded as the primary central nervous system targets of Amy because lesions of these brain regions completely abolish anorexigenic effect of Amy [275,276]. There is evidence that Amy also works on the mesolimbic DA circuits, however. mRNA for all components of AmyR complex and CTR immunoreactivity have been identified in VTA and NAcc [277,278], and ~63% of CTR-expressing VTA neurons co-express TH while ~12% of TH neurons co-express CTR [279]. Amy binding has been localized to the mesolimbic structures including the NAcc and VTA in autoradiography studies [280,281], and peripherally injected fluorescent-labeled Amy analog salmon calcitonin (sCT) was detected in the VTA and NAcc [282]. sCT also prevented the VTA-stimulated or drug-induced DA release in NAcc shell [283–285] and when administered directly into the VTA reduced food evoked phasic increase in NAcc core DA release [279]. Together with the anatomical findings, these results suggest that Amy may directly influence DA neurotransmission to regulate different behaviors. The involvement of Amy in the regulation of energy homeostasis and natural reward has been well characterized but the involvement of this peptide in the modulation of drug reward received little attention until recently.

Food and food reward:

Peripheral or ICV administration of AmyR agonists reduced food intake and body weight [286–289] whereas peripheral treatment with AmyR antagonist increased feeding [290]. Furthermore, both of these effects were primarily caused by a change in meal size [290,291] suggesting that Amy may facilitate meal-ending satiety. It was recently shown that the anorexigenic and body weight suppressing effects of Amy are true for both genders but are subject to some sex differences as the weight loss was only sustained in males after the discontinuation of long-term AmyR agonist treatment [292].

Consistent with its effects following peripheral administration, intra-VTA AmyR activation by sCT produced hypophagia that was mediated mainly by a reduction in meal size [277,279]. Blockade of AmyR increased food intake and attenuated intake-suppressive effects of peripherally administered sCT [277] suggesting physiological relevance of intra-VTA Amy signaling. sCT action in the VTA also decreased intake of palatable sucrose solution and HFD, again through a reduction in meal size, and decreased 24-hour body weight gain [277,279]. Furthermore, VTA AmyR activation reduced the intake of a palatable, non-nutritive sweetener [293] and reduced the motivation to work for sucrose reward [277] illustrating the peptide's involvement in regulation of food reward.

Amy action in the VTA may be preferentially targeted to regulation of fat intake as VTA CTR knockdown resulted in hyperphagia and increased body weight gain in rats fed HFD but not chow-fed animals [279] and VTA sCT produced a greater and more rapid suppressive effect on fat intake compared to sucrose [293]. Very little data is available on the action of Amy in NAcc, however. One study showed that Amy acts in the NAcc shell but not core to reduce food intake in food-deprived rats but this effect might have been due to an off-target action of Amy because changes in feeding were absent in a different experiment in which NAcc was targeted to avoid penetration of the lateral ventricle [294].

Mechanistically, Amy appears to modulate DA neurons to regulate feeding. For example, intra-VTA sCT administration attenuated food-induced DA release in the NAcc core [279] and NAcc core D1/D2R agonist blocked intake and body weight-suppressive effects of VTA AmyR activation in chow and HFD fed rats [279]. Further experiments will be necessary to determine how Amy regulates DA and other VTA neurons, however.

Alcohol intake and reward:

Amy signaling is involved in the expression of alcohol responses as shown by the attenuation of both acute and chronic alcohol-directed behaviors in rodents by systemic AmyR activation. For example, systemically administered sCT reduced alcohol-induced locomotor stimulation, alcohol-induced CPP, self-administration, and relapse drinking [284,295] with concurrent attenuation of alcohol-induced DA release in NAcc [284]. Similarly, sCT blocked alcohol-induced locomotor stimulation when administered into the VTA or NAcc shell and intra-VTA sCT decreased alcohol-induced DA release in the NAcc shell in mice and decreased alcohol intake in rats [282].

Effects on drugs of abuse:

Similar to the effects on food and alcohol-dependent NAcc DA release, peripheral treatment with sCT attenuated cocaine and nicotine-induced elevation in accumbal DA [285,296] and inhibited the expression of amphetamine, cocaine, and nicotine-induced hyperlocomotion [285,296–298]. Interestingly, unlike the effects on alcohol, peripheral sCT injection did not affect the rewarding properties or reward-dependent memory of cocaine or nicotine in the CPP paradigm [285,296] suggesting that Amy may regulate alcohol and stimulant drug reward differently. Local activation of VTA or NAcc shell AmyR reduced but did not fully inhibit cocaine-evoked locomotor stimulation, however [285], suggesting possible

involvement of other brain areas in Amy-mediated effects. Further experiments will be necessary to fully dissect the mechanism by which Amy influences drug reward.

Neurotensin

Neurotensin (NT) is an anorexigenic peptide released peripherally by intestinal enteroendocrine cells and the adrenal gland as well as centrally by neurons of several regions including the LH. This peptide signals through NT receptors (NTR1, NTR2, NTR3) and has been implicated in the regulation of many different physiological processes and behaviors including analgesia, blood pressure, body temperature, locomotion, and fluid and energy homeostasis. In this review, we will briefly go over the actions of NT in the mesolimbic system in the regulation of energy homeostasis and natural and drug reward but these topics are more thoroughly discussed in other prior reviews [299–301]).

Food and food reward:

Central and peripheral treatment with NT decreased food intake in fasted and sated rodents [302–304] and the anorectic effect of leptin was attenuated in NTR1 knockouts [305]. Substantial evidence suggests that NT interacts with the mesolimbic system to regulate behavior. Neuroanatomical studies support this interaction as NT-expressing neurons, primarily from the LH and medial and lateral preoptic areas, have been shown to project to the VTA [306–308]. Additionally, NT-immunoreactive axon terminals are found in direct contact with dendrites and perikarya of VTA TH+ neurons [309], and NT receptors, primarily NTR1, are expressed in the VTA neurons [310–312] where they are co-expressed with TH [313]. Intra-VTA injection of NT increased latency to eat and reduced food intake in fasted but not sated animals [314,315] and reduced operant responding for food [316]. Conversely, intra-NAcc injection of NT did not alter food intake [317]. Interestingly, ablation of VTA NTR1-expressing neurons in adult mice reduced body weight in chow-fed animals and protected the mice from HFD-induced obesity while increasing their intake of chow or HFD. This lean-promoting phenotype appeared to be caused by increased physical activity and energy expenditure [313]. Similar to chow and HFD, VTA NTR1 neuron ablated mice overconsumed sucrose but appeared to have unaltered motivation for sucrose. However, these mice failed to adjust their sucrose self-administration to energy sufficiency cues such as sucrose pre-feeding or leptin [313] suggesting that VTA NTR1 neurons may serve as a point of interaction between signals conveying metabolic status and motivated behavior.

Effects on drugs of abuse:

Central administration of NT or its analogs blocked amphetamine, cocaine, and nicotine-induced hyperactivity [318,319], decreased self-administration of METH and nicotine [320,321], prevented initiation and expression of sensitization to nicotine [322], and decreased alcohol preference and intake [323,324]. The effect on alcohol appears to be modulated by NTR1 as NTR1 null mice have increased ethanol intake, decreased sensitivity to ethanol-induced ataxia and these mice fail to respond to peripherally injected NT analog [323]. Much is unknown about the neural substrates of the NT action in regulation of drug

reward and future experiments are needed to determine the mechanisms underlying NT involvement in these behaviors.

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an anorexigenic incretin secreted from L cells of the small and large intestine and centrally from the preproglucagon neurons of the NTS. Several GLP-1 analogs, including Exendin-4 (Ex-4) and Liraglutide, are FDA-approved for treatment of type 2 diabetes and weight management because they increased insulin production, suppressed food intake, and produced weight loss (for review see [325–327]). In rodents, peripheral injections of Ex-4 decreased food intake and food and drug reward-associated behaviors [328–332], and a large body of data suggests that the mesolimbic circuitry is one of the neuroanatomical substrates of GLP-1's action in regulation of these behaviors. This is supported anatomically as both VTA and NAcc have been shown to contain GLP1-R mRNA [333], to house GLP-1 containing fibers [334,335], and to receive projections from GLP-1-expressing NTS neurons as identified by anterograde tracing experiments [334–336].

Food and food reward

The mesolimbic system is one of the targets of GLP-1 analogs in regulation of feeding as the reduction in feeding produced by systemic Ex-4 was attenuated by VTA pretreatment with a GLP-1R antagonist [337]. Injections of Ex-4 directly into the VTA also reduced intake of both palatable food and regular chow [329,335,337], and the effects on the palatable HFD intake were shown to be regulated in part by glutamatergic AMPA/kainate receptor signaling [337]. The intake of chow was only reduced in a fasted state or in *ad libitum* fed rodents when chow is the only caloric source, however [329]. Conversely, activation of VTA and NAcc core and shell GLP-1Rs in animals fed chow and HFD simultaneously decreased HFD intake while increasing chow intake [335,337,338] suggesting that GLP-1 plays a role in regulation of preference for high-energy food. Chemogenetic induction of GLP-1 release from NTS neurons in the VTA has also been shown to reduce HFD intake and to modulate this effect through a reduction in excitatory synaptic strength of VTA DA neurons that project to NAcc medial shell [339]. Ex-4 also decreased 1-hour sucrose intake when administered to the VTA and NAcc core but not NAcc shell suggestive of site-specific macronutrient intake regulation [335]. NAcc core administration of GLP-1R antagonist increased sucrose meal size and sucrose palatability but had no effect on licking for sweet saccharin solution suggesting that GLP-1 acts in the NAcc core to regulate the hedonic value of nutritive foods [340]. Peripheral and central administration of Ex-4 also strongly inhibits food reward-associated behaviors and the mesolimbic structures have been implicated in these responses [329] as shown by a reduction in the motivation to obtain sucrose reward in a progressive ratio paradigm by intra-VTA or intra-NAcc injections of Ex-4 [329]. Taken together, GLP-1 appears to act in the mesolimbic structures to decrease intake as well as the rewarding properties of hedonic foods with a smaller contribution to context-dependent regulation of homeostatic intake.

Alcohol intake and reward

Similar to its effects on food, peripheral injections of GLP-1 or Ex-4 have been shown to supress alcohol intake and to decrease multiple measures of alcohol-induced reward and seeking behaviors [331,341,342]. The effect on alcohol intake is dependent on the baseline consumption of alcohol as alcohol consumption was reduced by GLP-1R agonist only in alcohol-preferring rats while it remained unaffected in natural ‘nondrinkers’ [341,342]. The NAcc is one of the neuroanatomical substrates of GLP-1 mediated effects, as the same behavioral pattern was observed upon intra-NAcc Ex-4 treatment [343]. Unlike its effects on food, however, GLP-1 seems to modulate alcohol-related behaviors through NAcc shell and not core because NAcc shell but not core Ex-4 injections decreased alcohol intake [343,344] as well as alcohol-induced locomotor response and alcohol CPP while leaving chow intake and body weight unaffected [343]. These results suggest that anatomically distinct portions of the mesolimbic circuitry may modulate homeostatic feeding and alcohol-directed behaviors. The effects of GLP-1 in the VTA on alcohol-related behaviors are somewhat conflicting. Intra-VTA Ex-4 has been shown to decrease alcohol intake in rats [342] but this effect on intake could not be replicated by another group, although they did report a decrease in alcohol-induced locomotor behavior [343]. Interestingly, VTA effects were only produced by posterior and not anterior VTA treatment with Ex-4 [343] suggesting that GLP-1 acts on a specific VTA sub-circuit to regulate alcohol-directed behaviors. Taken together, GLP-1 acts on the structures of the mesolimbic system to attenuate alcohol intake and reward and this action and circuitry involved may be distinct from that used to regulate food-associated behaviors.

Effects on drugs of abuse

Systemic or central administration of GLP-1R agonists attenuate addiction-related effects of cocaine, amphetamine, and nicotine including intake, operant behavior, and CPP [330,332,345–349]. In the VTA, Ex-4 reduced cocaine self-administration [350] and primed reinstatement of cocaine seeking [351] while VTA GLP-1R knockdown increased cocaine self-administration [350]. Similarly, Ex-4 has been shown to act in both NAcc shell and core to reduce cocaine-primed reinstatement of drug seeking [352]. Interestingly, unlike GLP-1’s effects on the regulation of intake and rewarding aspects of food, alcohol, cocaine, amphetamine, and nicotine, peripherally administered GLP-1R agonist failed to decrease the addiction-related behavioral effects of opioids including CPP, withdrawal, hyperlocomotion, or self-administration [353] suggestive of differences in the mechanisms regulating effects of opioids and. other natural and drug rewarding substances.

Summary/Conclusions

Multiple peptides and hormones that play important roles in the control of feeding and energy homeostasis can interact with the mesolimbic DA system to regulate an array of DA-dependent behaviors, including food, drug, and social reward (Fig. 1). In some cases, the effects of these peptides are similar across different rewards, but for others there appear to be distinct effects of the peptides on different types of reward (Fig. 1). Furthering our understanding of how these feeding-related peptides interact with mesolimbic circuits to regulate behavior may help identify how changes in feeding and weight alter mesolimbic DA

system-dependent behaviors and may allow for new approaches to treat disorders associated with these systems.

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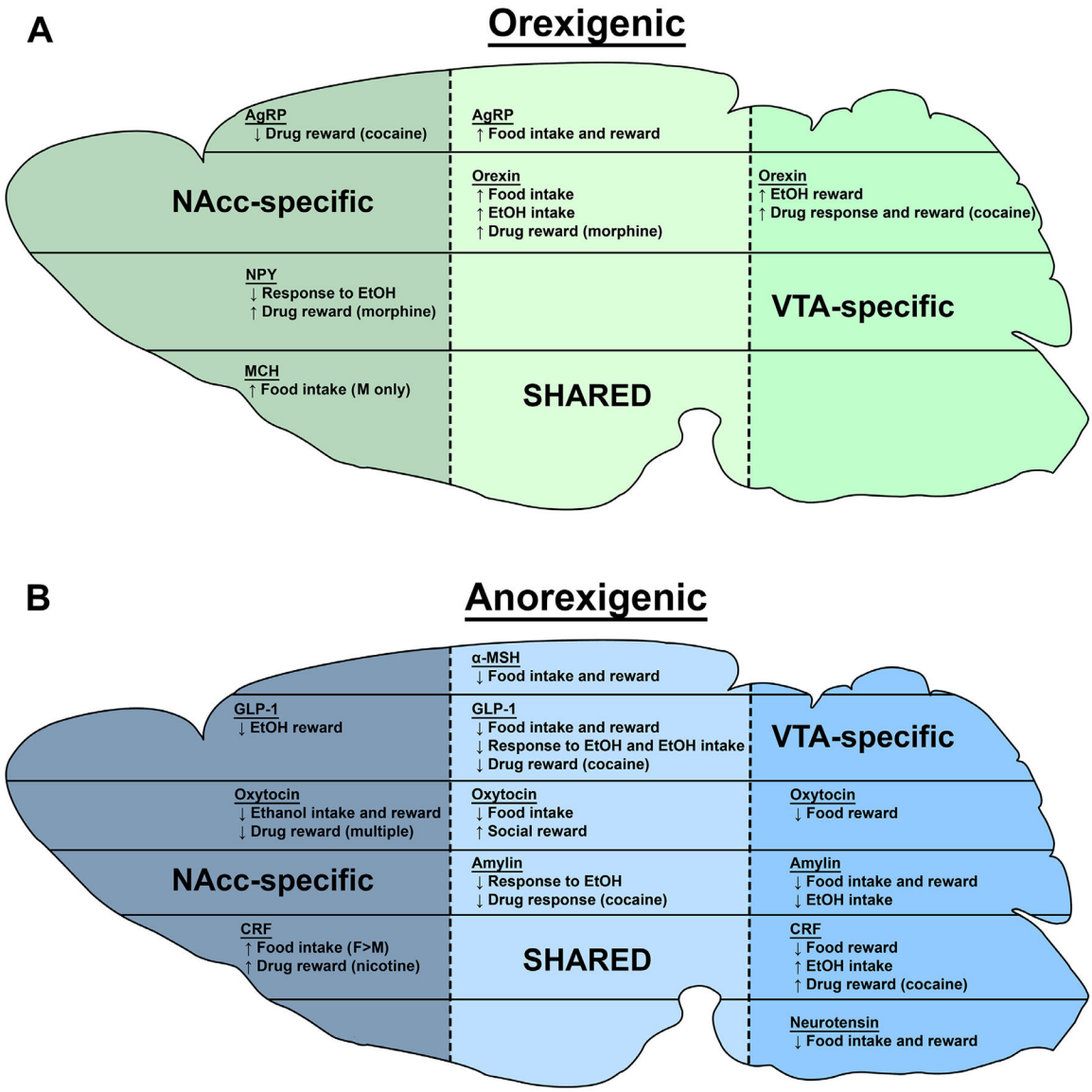

Fig. 1.

Summary of the behavioral effects of the mesolimbic system action of peptides and hormones reviewed in this manuscript. Sagittal outline of the brain in green summarizes the effects of intra-NAcc and intra-VTA actions of orexigenic peptides (A) while the section in blue summarizes the effects of anorexigenic peptides (B) and hormones on feeding as well as food, drug, and social reward. In general, “intake” refers to free consumption, “reward” refers to behaviors measured by paradigms such as self-administration and CPP, and “response” refers to behaviors such as substance-induced locomotion. “NAcc-“and VTA-specific sections describe effects produced exclusively in that area (which sometimes were due to the lack of response and in other cases due to lack of testing) whereas the SHARED section contains common effects produced by peptide/hormone action in the two brain regions. Abbreviations used: EtOH-alcohol; M-male; F-female.

Table 1

Overview of studies showing effects of discussed peptides and hormones on food, alcohol, drug, and social behavior.

Peptide	Brain area	Manipulation	Behavioral effect	Citation
α-MSH	VTA	Intraparenchymal MCR agonist injection	Reduced the intake of chow and sucrose	(Roseberry, 2013; Yen and Roseberry, 2014)
			Decreased sucrose self-administration	(Shanmugarajah et al., 2017)
		Intraparenchymal MC3R agonist injection	Increased sucrose self-administration but not free feeding on sucrose.	(Pandit et al., 2016)
		Chemogenetic activation of MC3R-expressing neurons	Decreased feeding in female mice	(Dunigan et al., 2021)
	NAcc	Intraparenchymal MC4-R agonist injection	Decreased feeding	(Lerma-Cabrera et al., 2012)
		Intraparenchymal α-MSH injection	Decreased motivation for sucrose	(Pandit et al., 2015)
AgRP	VTA	Intraparenchymal MCR antagonist injection	Increased chow intake	(Roseberry, 2013)
			Increased sucrose self-administration	(Shanmugarajah et al., 2017)
		Chemogenetic inhibition of MC3R-expressing neurons	Decreased feeding in male mice	(Dunigan et al., 2021)
	NAcc	Intraparenchymal MC4-R antagonist injection	Increased feeding	(Lerma-Cabrera et al., 2012)
		Intraparenchymal AgRP or MCR antagonist injection	Increased motivation for sucrose	(Pandit et al., 2015)
			Blocked reinforcing, motivational and sensitizing effects of cocaine	(Hsu et al., 2005)
	Global	MC3R knockout and re-expression	Sex-dependently altered sucrose preference and DA turnover.	(Lippert et al., 2014).
			Altered food self-administration under FR1 and PR conditions in food-restricted mice with a reversal in PR responding following MC3R re-expression in DA neurons.	(Mavrikaki et al., 2016)
NPY	NAcc	Constitutive activation of NAcc NPY2R	Reduced expression of ethanol-induced behavioral sensitization	(Hayes et al., 2012)
		Intraparenchymal NPY or NPY1R agonist injection	Increased ethanol self-administration directly into the posterior VTA.	(Borkar et al., 2016)
				(Desai et al., 2013)
			Potentiated the rewarding effect of morphine.	(Wang et al., 2020)
			Prolonged the extinction period following chronic morphine exposure	
		Intraparenchymal NPY5R antagonist injection	Reduced morphine extinction period	(Wang et al., 2020)

Peptide	Brain area	Manipulation	Behavioral effect	Citation
CRF	VTA	Intraparenchymal CRF injection	Reduced motivation for food reward	(Wanat et al., 2013)
			Reinstated lever pressing for cocaine	(Wang et al., 2005; Wang et al., 2007)
		Intraparenchymal CRF antagonist injection	Blocked foot shock-induced reinstatement of cocaine seeking.	(Wang et al., 2005)
				(Boyson et al., 2014).
			Prevented dopaminergic cross-sensitizations and escalated cocaine self-administration.	
		Intraparenchymal CRFR1 antagonist or CRFR2 agonist injection	Decreased binge-like ethanol drinking (drinking in the dark)	(Rinker et al., 2017; Sparta et al., 2013)
		Intraparenchymal CRFR1 antagonist	Reduce alcohol consumption in an intermittent access two-bottle choice paradigm.	(Hwa et al., 2013)
				(Hwa et al., 2016)
				(Grieder et al., 2014).
			Reduced social defeat stress-enhanced ethanol drinking.	
			Prevented anxiety-like behavior during nicotine withdrawal.	
		ShRNA-mediated knockdown of CRFR1	Reduced cue-induced cocaine seeking but not cue-induced sucrose seeking	(Chen et al., 2014)
	NAcc	Intraparenchymal CRF injection	Enhanced the ability of Pavlovian reward cues to trigger instrumental performance for sucrose reward	(Peciña et al., 2006)
		CRF overexpression	Increased operant responding to nicotine and increased food intake (females> males)	(Uribe et al., 2020).
MCH	NAcc	Intraparenchymal MCH injection	Increased feeding (only in males) Restored feeding in *Pmch* null mice to wild-type levels	(Georgescu et al., 2005; Terrill et al., 2020)
				(Mul et al., 2011).
		Intraparenchymal MCHR1 antagonist injection	Decreased feeding	(Georgescu et al., 2005)
Orexin	VTA	Intraparenchymal OX-A injection	Increased chow, HFD and sucrose intake.	(Terrill et al., 2016)
			Attenuated intragastric nutrient-induced hypophagia.	(España et al., 2011)
				(Harris et al., 2005; Wang et al., 2009)
			Promoted cocaine self-administration. Reinstated previously extinguished morphine and cocaine preference.	
		Intraparenchymal OX-1R antagonist injection	Attenuated orexigenic effects of ICV ghrelin.	(Cone et al., 2014)
				(Olney et al., 2017)
			Blunted binge-like ethanol intake.	(Borgland et al., 2009; España et al., 2010)

Peptide	Brain area	Manipulation	Behavioral effect	Citation
			Reduced cocaine self-administration.	
			Prevented acquisition of locomotor sensitization to cocaine.	(Borgland et al., 2006)
				(James et al., 2011)
			Attenuated cue-induced cocaine reinstatement.	
		Intraparenchymal OX-1R/OX-2R antagonist injection	Attenuated alcohol self-administration	(Srinivasan et al., 2012)
	NAcc	Intraparenchymal OX-A injection	Increased feeding	(Thorpe and Kotz, 2005)
			Increased the hedonic impact of sucrose taste and increased palatable food intake	(Castro et al., 2016)
		Intraparenchymal OX-1R antagonist injection	Decreased alcohol intake in excessive but not moderate drinkers	(Lei et al., 2019; Lei et al., 2016)
				(Qi et al., 2013)
			Attenuated stress-induced morphine reinstatement	
Oxytocin	VTA	Intraparenchymal OT injection	Decreased chow intake at acute time points.	(Wald et al., 2020)
				(Mullis et al., 2013)
			Decreased sucrose intake.	(Wald et al., 2020)
			Reduced food motivation and food seeking. (Mullis et al., 2013; Wald et al., 2020)	(Song et al., 2016).
				(Borland et al., 2018)
			Reduced place avoidance for the social interaction chamber.	
			Decreased the frequency of seeking social interaction in Operant Social Preference task.	
		Optogenetic stimulation of PVN OT axon terminals	Promoted sociability.	(Hung et al., 2017)
		Intraparenchymal OTR antagonist injection	Increased sucrose intake.	(Mullis et al., 2013)
			Increased the frequency of entering social interaction chambers in Operant Social Preference task.	(Borland et al., 2018)
	NAcc	Intraparenchymal OT injection	Decreased chow intake in deprived conditions and the consumption of palatable nutritive and non-nutritive sweet solutions.	(Herisson et al., 2016)
				(Baracz et al., 2012; Cox et al., 2017)
				(Ibragimov et al., 1987; Weber et al., 2018)
			Attenuated METH-induced CPP, drug seeking and demand.	
			Inhibited cocaine seeking and heroin self-administration.	

Addict Neurosci. Author manuscript; available in PMC 2023 May 22.

Peptide	Brain area	Manipulation	Behavioral effect	Citation
		OTR overexpression	Reduced ethanol preference, ethanol intake, and reinstatement of ethanol conditioned place preference.	(Bahi, 2015; Bahi et al., 2016)
		Intraparenchymal OTR antagonist injection	Prevented social CPP.	(Dolen et al., 2013)
Amylin	VTA	Intraparenchymal AmyR agonist injection	Decreased the intake of chow, sucrose, and HFD primarily through a reduction in meal size.	(Mietlicki-Baase et al., 2015; Mietlicki-Baase et al., 2013b)
				(Mietlicki-Baase et al., 2017)
			Decreased the intake of palatable, non-nutritive sweetener.	(Mietlicki-Baase et al., 2013b)
				(Kalafateli et al., 2021b)
			Decreased the motivation to work for sucrose reward.	(Kalafateli et al., 2021a)
			Blocked alcohol-induced locomotor stimulation and decreased alcohol-induced DA release in the NAcc shell in mice and decreased alcohol intake in rats.	
			Decreased cocaine-evoked locomotor stimulation.	
		Intraparenchymal AmyR antagonist injection	Increased food intake.	(Mietlicki-Baase et al., 2013b)
		VTA CTR knockdown	Produced hyperphagia in HFD-fed animals.	(Mietlicki-Baase et al., 2015)
	NAcc	Intraparenchymal AmyR agonist injection	Blocked alcohol-induced locomotor stimulation.	(Kalafateli et al., 2021b)
				(Kalafateli et al., 2021a)
			Decreased cocaine-induced locomotor stimulation.	
Neurotensin	VTA	Intraparenchymal NT injection	Increased latency to eat and reduced food intake in fasted animals.	(Cador et al., 1986; Hawkins, 1986)
				(Kelley et al., 1989)
			Reduced operant responding for food.	
		NTS1R-expressing neuron ablation	Increased the intake of chow, sucrose, and HFD.	(Woodworth et al., 2017).
GLP-1	VTA	Intraparenchymal GLP-1R agonist injection	Reduced the intake of palatable food.	(Alhadeff et al., 2012)
			Reduced chow intake in fasted animals or when chow was the only caloric source.	(Dickson et al., 2012).
				(Alhadeff et al., 2012; Mietlicki-Baase et al., 2014; Mietlicki-Baase et al., 2013a)
			Decreased HFD intake while increasing chow intake in animals fed both diets simultaneously.	(Alhadeff et al., 2012).
				(Dickson et al., 2012).

Peptide	Brain area	Manipulation	Behavioral effect	Citation
			Decreased 1hr sucrose intake.	(Shirazi et al., 2013)
			Decreased the motivation to obtain sucrose reward.	(Vallöf et al., 2019).
				(Schmidt et al., 2016)
			Decreased alcohol intake.	(Hernandez et al., 2018)
			Decreased alcohol-induced locomotor behavior.	
			Reduced cocaine self-administration.	
			Reduced cocaine-primed reinstatement.	
		Chemogenetic induction of GLP-1 release from NTS terminals	Reduced HFD intake.	(Wang et al., 2015)
	NAcc	Intraparenchymal GLP-1R agonist injection	Decreased HFD intake while increasing chow intake in animals fed both diets simultaneously.	(Alhadeff et al., 2012; Mietlicki-Baase et al., 2014; Mietlicki-Baase et al., 2013a)
				(Alhadeff et al., 2012).
			Decreased 1hr sucrose intake.	(Dickson et al., 2012).
			Decreased the motivation to obtain sucrose reward.	(Vallöf et al., 2019)
				(Hernandez et al., 2019).
			Decreased alcohol consumption in alcohol-preferring animals only.	
			Decreased alcohol-induced locomotor response and alcohol CPP.	
			Reduced cocaine-primed reinstatement.	
		Intraparenchymal GLP-1R antagonist injection	Increased sucrose meal size and sucrose palatability.	(Dossat et al., 2013)