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Review

Lateral hypothalamic area neuropeptides modulate ventral tegmental area dopamine neurons and feeding

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ABSTRACT

Understanding how the brain coordinates energy status with the motivation to eat is crucial to identify strategies to improve disordered body weight. The ventral tegmental area (VTA), known as the core of the mesolimbic system, is of particular interest in this regard because it controls the motivation to consume palatable, calorie-dense foods and to engage in volitional activity. The VTA is largely composed of dopamine (DA) neurons, but modulating these DA neurons has been alternately linked with promoting and suppressing feeding, suggesting heterogeneity in their function. Subsets of VTA DA neurons have recently been described based on their anatomical distribution, electrophysiological features, connectivity and molecular expression, but to date there are no signatures to categorize how DA neurons control feeding. Assessing the neuropeptide receptors expressed by VTA DA neurons may be useful in this regard, as many neuropeptides mediate anorexic or orexigenic responses. In particular, the lateral hypothalamic area (LHA) releases a wide variety of feeding-modulating neuropeptides to the VTA. Since VTA neurons intercept LHA neuropeptides known to either evoke or suppress feeding, expression of the cognate neuropeptide receptors within the VTA may point to VTA DA neuronal mechanisms to promote or suppress feeding, respectively. Here we review the role of the VTA in energy balance and the LHA neuropeptide signaling systems that act in the VTA, whose receptors might be used to classify how VTA DA neurons contribute to energy balance.

1. The importance of feeding and energy balance

Perhaps the most frequent behaviors that animals engage in are eating and drinking. The physiological processes required for life (e.g. thermogenesis, respiration, waste filtration, movement etc.) constantly consume onboard energy and water, so these resources must be replenished. Since energy (from food) and water can only be obtained via ingestion, survival depends on detecting the need for these resources and motivating the behavior to seek and consume them. Multiple neural circuits that contribute to feeding have been characterized, and serve to tune feeding to the environmental, interoceptive and emotional state of the organism [1,2]. Yet, despite the fundamental necessity of ingestion, the neural mechanisms by which the brain modulates the motivation to seek and consume food are yet to be fully elucidated. Understanding these processes is paramount for understanding basic biology and survival.

Feeding implicitly impacts “energy balance”, a term used to describe the linked relationship of energy intake and energy expenditure that has important ramifications for health. Energy intake refers to the calories obtained from ingested food and fluids, while energy expenditure refers to the energy that is consumed through basal metabolic rate, thermogenesis and physical activity [3]. Body weight is a “readout” of energy balance, since it depends on the amount of calories consumed to calories burned. Changes in the extent of feeding or energy expended accordingly change body weight. There are periods when it is advantageous to be “imbalanced”. For example, during development, more calories must be consumed than expended to support growth, including increased body weight. In adulthood, energy balance should be more stable, such that day to day energy intake and output are relatively equal, and weight is maintained [3]. Even in this state, however, dynamic fluctuations of energy intake occur across the day as energy consumption creates need to replenish energy reserves. Energy

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deficiency registers as hunger and increases the drive to find and ingest food. Feeding restores satiety, which reduces the drive to eat while enabling for locomotor activity, thermogenesis and other energy dependent behaviors [3]. These actions are largely orchestrated by neurons in the hindbrain and mediobasal hypothalamus, collectively referred to as the homeostatic system. Thus, cues of energy status inform the body about food "need" and promote appropriate behaviors to resolve any energy imbalance.

Yet, feeding may also occur in the absence of need, and can threaten energy balance. For example, despite being satiated from a meal we might still eat dessert simply because it tastes good. Hence, external cues and/or the anticipated reward from food can potentiate excess caloric intake, and accordingly, weight gain. Overweight and obesity are energy balance disorders that develop due to elevated consumption of palatable and calorie-dense foods. Since overconsumption often occurs in combination with sedentary lifestyle and reduced energy expenditure, this leads to a "perfect storm" for weight gain [4]. More than one-third of US adults are obese, placing them at increased risk to develop chronic co-morbidities such as cardiovascular diseases and type-2 diabetes that diminish life quality and length [5,6]. Curbing so called "reward feeding" is therefore a major goal to treat and prevent the development of overweight and obesity. While there are some pharmacotherapies to support acute weight loss, they are minimally effective in the long-term to restrain feeding, and have yet to stem the rising disease incidence [4,7,8]. As a result, combined diet and exercise remain the most widely prescribed treatment for overweight and obesity. However, dieting increases appetitive drive that can spur overeating such that most individuals regain weight with time [9–13]. Since altered motivation and drive to eat negatively impacts health it is vital to understand how the brain coordinates feeding behavior, to pinpoint how and why it goes awry in disease states.

1.1. The ventral tegmental area modulates feeding

The ventral tegmental area (VTA) is well known to modify intake of pharmacological and natural rewards, including food. While the neural mechanisms of this process remain incompletely understood, the VTA appears to coordinate energy status and external cues so as to influence feeding behavior. The VTA is located near the base of the midbrain and it contains dopamine (DA) neurons (~60%-65%), GABA neurons (~30%-35%) and a small subset of glutamate neurons (~2%-3%) [14,15] (Fig. 1). Given these proportions, it is of little surprise that most research has focused on the role of the DA neurons within the VTA and

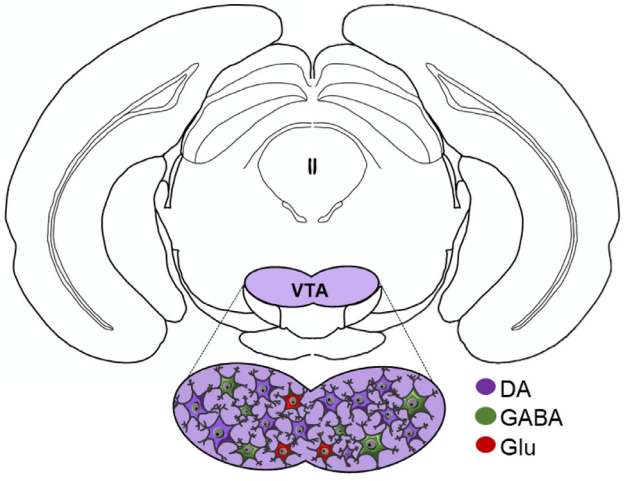


Fig. 1. Neuronal composition of the VTA illustrated on a coronal section of mouse brain. The VTA is primarily composed of DA neurons, followed by GABA and glutamate (Glu)-containing neurons.

their roles in feeding behaviors. However, recent work confirms that some subpopulations of VTA GABA neurons[16–18] and VTA glutamate neurons [18–20] can modify behaviors independently of DA neurons, some of which are relevant to feeding. VTA glutamate neurons are located primarily in the rostral and medial portions of the VTA, and their activation has been shown to drive conditioned place preference, reinforcement of instrumental behavior and aversive conditioning in mice [18–20]. GABA expressing neurons also have a role in aversion [17,21], but, on the other hand, are distributed throughout the VTA [16,22,23] and have been shown to suppress the activity and excitability of neighboring DA neurons [16].

Owing to their abundance, however, VTA DA neurons are the most studied VTA population, and are involved in an array of motivated behaviors [21,24–26], from positive and negative reinforcement, decision making, working memory, stimulus salience and aversion [27–32]. VTA DA neurons also respond to cues that predict rewards [33] and DA is a key substrate in the incentive and reinforcing aspects of food intake [34–38], locomotor activity and body weight [39]. This participation of VTA DA neurons in so many actions suggests a degree of functional heterogeneity, and has prompted speculation on whether there are subsets of DA neurons to mediate specific behaviors – including, perhaps, specific feeding behaviors. In potential support of this idea, experimental activation of VTA DA neurons has yielded a "mixed bag" of feeding responses, from enhancement to suppression [40–43]. One possible explanation may be the methods used to target and activate the VTA DA neurons, which at least in some cases only activated a portion of all VTA DA neurons [40,41]. It is possible, therefore, that these experiments manipulated subsets of VTA DA neurons that differ in how they control feeding. Similarly, while not examining feeding specifically, recent work demonstrates that modulating the activity of subsets of VTA DA neurons differentially modifies behavioral reinforcement [43]. Moreover, manipulation of specific subsets does not always produce the same behavior as manipulation of all VTA DA neurons [43]. In combination, these findings support examination of methods to classify VTA DA neurons, to identify whether there are subsets with different roles in regulating feeding.

There has been a recent explosion of work directed toward identifying subsets of VTA DA neurons. They have been geographically classified by their distribution across the VTA; DA neurons in the ventral VTA for example, are excited by noxious foot shocks, in contrast to dorsal VTA DA neurons, which are inhibited [29,44]. VTA DA neurons can also be differentiated according to their electrophysiological firing properties [45,46]. As of yet, however, there is no consensus on specific electrophysiological or anatomical signatures that predict how VTA DA neurons modify feeding. However, VTA DA neurons can also be described by their anatomical inputs and projections [43,47,48], and the latter may provide insight into functional subsets and feeding control. The majority of VTA DA neurons project to the nucleus accumbens (NAc), where DA release has been shown to control the "wanting" of pharmacological and natural rewards and the goal-directed behaviors to obtain them (for review on VTA DA innervating NAc and its influence in motivation see Salamone and Correa, 2012) [32]. Other VTA DA neurons project to the prefrontal cortex, amygdala, hippocampus and other brain regions that alter top-down control, anxiety and learning, all of which can impact the extent of feeding [49]. Given this range in projection targets, it seems plausible that the differences in VTA DA neuronal connectivity might track with separate functionality, and possibly differentiable molecular signatures. Recent work supports that there is variable gene expression across VTA DA neurons, and the existence of subpopulations with differing expression of transcription factors, channels, DA related genes and receptors for neurotransmitters, hormones and neuropeptides [50–52].

Of these, peptide receptors have garnered considerable interest to parse VTA DA neurons that might influence feeding. Peptide signals can reach the VTA via two routes: via the circulation (as peptide hormones) and through being released from neurons (as neuropeptides). For

example, circulating cues of energy status, such as the peptide hormones insulin, leptin and ghrelin act directly upon hypothalamic neurons as well as on VTA neurons [53,54]. Expression of these hormone receptors on VTA DA neurons can identify subsets of neurons that likely contribute to anorectic or orexigenic responses. Yet, hypothalamic regions have more rapid access to circulating cues than the VTA, due to being adjacent to the "leaky" median eminence that permissively allows circulating factors access to the brain. By contrast, the VTA lies deep within the brain and far from the median eminence. Hence, the VTA is capable of directly responding to circulating peptide cues of energy status, but is not considered to be the "first-responder" to them that can rapidly inform the direction of feeding.

The VTA is also modulated by neurons in other brain areas that release neurotransmitters and neuropeptides to VTA neurons. In order for VTA neurons to intercept these released messages they must express the cognate receptors. For example, VTA neurons express classical neurotransmitter receptors, and receive excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmitter input from various areas in the brain (for a review on specific glutamatergic or GABAergic inputs onto specific neuronal populations in the VTA see Morales and Margolis, 2017) [45]. GABA and glutamate are important modulators of VTA DA neuronal activity but are also critical in regulating a wide array of physiology and aren't solely linked with changing feeding. By contrast, some neuropeptides are directly implicated in modulating feeding, may be anorectic or orexigenic in nature, and mediate these actions via their cognate peptide receptors. Indeed, reports have begun to emerge that classify subsets of VTA DA neurons via their expression of neuropeptide receptors, and at least some of these track with specific projection targets and control of behavioral reinforcement [43,55]. These early studies have only categorized neuropeptide-receptor expressing neurons without assessing the role of the neuropeptide signals on VTA DA subsets nor from where the neuropeptides originated. Defining the neurons that release feeding-modulating neuropeptides to the VTA, as well as which VTA DA neurons respond to them, holds promise to reveal the mechanisms underlying feeding.

1.2. The lateral hypothalamic area engages the VTA to modify feeding

The VTA receives neuronal projections from various areas in the brain, but the three main input contributors are the ventral pallidum, dorsal raphe nucleus and hypothalamus [56,57]. Of all of the subregions of the hypothalamus, the VTA receives its densest inputs from the lateral hypothalamic area (LHA) [56], a region well-studied for its role in energy balance and neuropeptide expressing neurons [58]. The LHA is viewed as a coordinating center, since it receives afferent input concerning internal status (e.g. energy, osmolality, temperature, pH, etc.) and sends projections to brain sites capable of modifying behavior to address any homeostatic deviations (For a review of the LHA control of energy balance, see Kurt, Woodworth and Leinninger, 2017). While the LHA projects widely throughout the brain to orchestrate homeostasis, the LHA VTA connection is specifically linked with coordinating energy sensing with goal-directed feeding behavior. Indeed, lesion of either the LHA or the VTA cause similar deficits in feeding, while stimulation of either site can incite ingestion [59–65]. Moreover, LHA neurons directly and indirectly receive cues of energy status, and then accordingly modulate the activity of target neurons (including those in the VTA) to modify feeding [66]. Thus, the LHA works in concert with the VTA to coordinate energy sensing and ingestion [49,56,57].

The nature of LHA communication with the VTA is complex, however, since the LHA exhibits a high degree of cellular heterogeneity. There are multiple molecularly distinct neuronal subpopulations within the LHA that are implicated in the control of diverse physiology, including sleep/arousal, reward, food intake, liquid intake, locomotor activity, stress, and response to inflammation [67]. LHA neurons can be molecularly classified by their transmitters, and typically contain one classical neurotransmitter (either excitatory glutamate or inhibitory GABA) along with several neuropeptides [68–72]. Both of these types of signals can be released to target neurons in the VTA, and hence LHA classical transmitters and neuropeptides can impact VTA-mediated behaviors [54]. This leads to enormous complexity in assessing how any "LHA neuron" that projects to the VTA actually modulates feeding, as it could simultaneously release a mix of signals that mediate different effects. Intriguingly, at least some projection-specified subsets of VTA DA neurons respond differently to the same LHA-derived signals, though the mechanism of how this occurs is yet unclear [73]. One possibility is that subsets of VTA DA neurons differentially express receptors for classical transmitters or neuropeptides, or express them in different proportions that influences what message is received. Since neurotransmitter and neuropeptide signals differ in important ways, including their mechanism and site of release, it is important to consider these features in regard to how LHA signals modulate VTA neurons.

Classical neurotransmitters are released at the active zone of the axon terminal, then diffuse across the synaptic cleft (a magnitude of nanometers) to bind to ionotropic receptors on the post-synaptic neuron. Classical transmitter binding to these receptors mediates rapid changes in ionic current and activity of the postsynaptic neurons. Signaling is terminated by enzymatic degradation of the classical transmitter or active reuptake, either of which reduce the amount of transmitter in the synaptic cleft available to bind to postsynaptic receptors. LHA classical neurotransmitter input to the VTA can support a variety of behaviors, depending on context. For example, experimental activation of all LHA GABAergic neurons that project to the VTA promotes feeding [72,74]. However, LHA GABA neurons show heterogeneity in their neuronal responses during food seeking and consumption [75], suggesting that not every GABA neuron is functionally the same. Indeed, it is now clear that there are multiple subpopulations of GABA neurons within the LHA that differ in their co-expressed neuropeptide content [76]. Moreover, subsets of LHA GABA neurons appear to be activated by distinct peripheral stimuli [77]. Thus, while many LHA neurons that project to the VTA release GABA, it is physiologically unlikely that all LHA GABA neurons are activated at the same time, or that they all exert the same effects within the VTA. The LHA also contains glutamatergic neurons, some of which project to the VTA and can stimulate feeding and arousal [67,78–80]. However, many LHA glutamatergic neurons project to the lateral habenula, and their stimulation suppresses food intake [81]. Thus, the effect that an LHA neuron will have on the VTA or feeding behavior cannot be predicted by its classical transmitter content alone. Hence, the expression of GABA or glutamate receptors are not likely to distinguish VTA DA neurons and their control of feeding.

The neuropeptide content of LHA neurons is a more reliable predictor of how they engage the VTA and modulate feeding. Indeed, LHA subpopulations can be differentiated by their neuropeptide expression, which hints that they exert distinct, neuropeptide-determined effects on target neurons expressing the cognate receptors. For this reason, LHA neurons are typically referred to by their neuropeptide content, such as "Orexin/Hypocretin neurons (OX/HCRT)" or "Melanin Concentrating Hormone (MCH)" neurons. Although classical neurotransmitters and neuropeptides can be released by the same neurons, they are fundamentally different signaling molecules. (For a review on neuropeptides and their involvement in modulating the central nervous system, see van del Pol, 2012.) Briefly, neuropeptides are short sequences of amino acids (3-36) that are synthesized in the soma [82,83]. They are packaged into dense core granules for release, which can occur at any part of the membrane and is not restricted to the active zone (as is the case for neurotransmitters) [82]. In addition, neuropeptides can diffuse much further than classical transmitters, in the magnitude of microns. Neuropeptides are also thought to have a long extracellular half-life, and so can have prolonged actions on target neurons [82]. Generally, neuropeptides bind to G protein-coupled receptors (GPCRs) that can be expressed on soma, dendrites, and axon terminals, depending on receptor

subtype. Neuropeptide binding to receptors modulates intracellular signaling pathways and phosphorylation of several target proteins that can lead to long-term changes in gene transcription and neuronal function [82]. They can also impact the likelihood of a neuron to be activated in response to classical transmitters [82]. Thus, neuropeptides are considered neuromodulators because their release can broadly affect many neurons in the vicinity and invoke lasting changes in function and activity. However, there are numerous neuropeptides, and each can differentially regulate distinct populations of neurons and behaviors. For example, LHA neuropeptides such as MCH, OX/HCRT and galanin promote feeding, whilst the neuropeptide neurotensin (Nts) suppresses feeding [58]. This range of neuropeptide-regulation indicates that they utilize different mechanisms to modify feeding. Because VTA neurons receive and can respond to these neuropeptides, it is possible that the distribution of neuropeptide receptors on VTA neurons could be used to distinguish VTA populations that differentially modify feeding behavior.

To be clear, neuropeptides are not just limited to the LHA, as they are expressed in many neuronal populations throughout the brain [82]. Moreover, neuropeptides throughout the brain have been implicated in disorders of excessive consumption, including drug and alcohol abuse and eating disorders [83], and at least some of their effects are mediated via the VTA. However, it is notable that many LHA neuropeptide-expressing neurons have been shown to modulate behavior via directly engaging the VTA, including feeding, drinking and physical activity. The varied neuropeptide release from LHA neurons to the VTA indicates a potential mechanism by which target VTA DA neurons might differ: in their expression of the cognate neuropeptide receptors. Some subsets of VTA DA neurons have already been classified by their expression of a neuropeptide receptor, and some of these are receptors for neuropeptide ligands released from the LHA [43,55]. However, it is unlikely that subpopulations of VTA DA neurons are defined by a single neuropeptide receptor. Indeed, VTA DA neurons almost certainly receive multiple, simultaneous peptidergic inputs from the LHA and/or other areas, via which they coordinate dopaminergic output in target regions and modulation of behaivor [54]. It is possible that some VTA DA neurons might express a suite of receptors that are indicative of how they modify feeding behavior. Thus, deciphering the neuropeptide signaling systems that mediate hypothalamic-VTA interactions could provide insight into how the brain coordinates energy need and ingestive behavior. Below, and summarized in Fig. 2, we review the evidence for LHA neuropeptide regulation of the VTA, given the known importance of the LHA→VTA connection to feeding behavior. Specifically, we address which of the associated neuropeptide receptors might discriminate VTA DA subsets with unique contributions to feeding and body weight.

2. Lateral hypothalamic area neuropeptides that modulate VTA DA neurons

2.1. Orexin/hypocretin

LHA neurons expressing the neuropeptides orexin/hypocretin (OX/HCRT) project widely throughout the brain, including to VTA DA neurons [84]. Interestingly, OX/HCRT is not a stimulator of food intake *per se*, but a stimulator of arousal, which in turn promotes feeding [66,85–87]. OX/HCRT promotes intake of natural and drug rewards via actions on VTA neurons [69,88–92]. Indeed, OX/HCRT neurons are activated during cue-induced feeding, and they in turn activate VTA DA neurons and promote DA release into the NAc and PFC [69,88,89]. OX/HCRT signaling in the VTA promotes neuronal activity by enhancing excitation and suppressing inhibition of DA neurons [69,93,94]. This promotes DA release necessary to drive reward seeking [89–92]. Thus, OX/HCRT acts via modulating VTA DA neurons to promote the ingestion of highly salient substances, including goal-directed responding for palatable foods. These responses are attenuated by pharmacologically

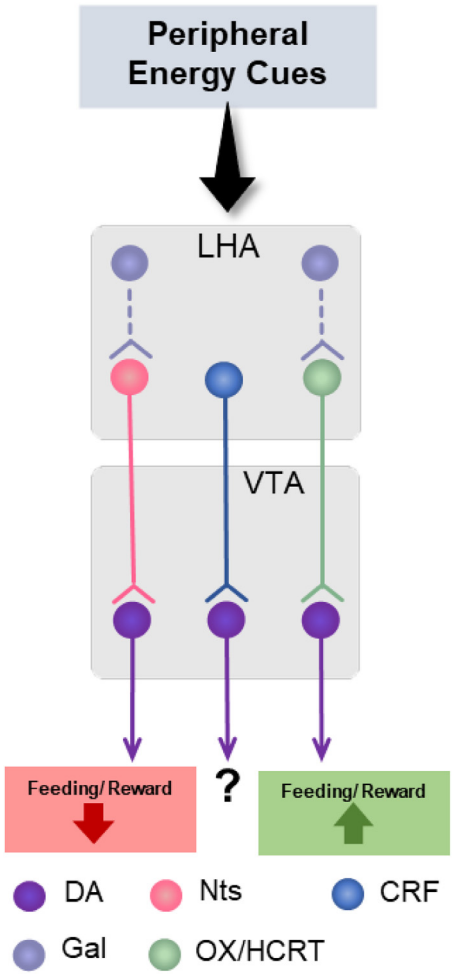


Fig. 2. Summary of LHA neuropeptidergic input to VTA DA neurons. VTA DA neurons are directly innervated by neuropeptide-containing neurons from the LHA that can decrease or promote feeding and reward behaviors. From the LHA, projecting neurons include neurotensin (Nts), corticortropin releasing factor (CRF) and orexin/hypocretin (OX/HCRT). Although CRF neurons also project to VTA DA neurons, their contribution to feeding/reward behavior is still not clear. Galanin (Gal) does not directly innervate DA neurons but rather projects to OX/HCRT neurons within the LHA that may project to the VTA.

antagonizing OX/HCRT receptors, indicating that the OX neuropeptide is a key signal form OX/HCRT neurons that is necessary to promote feeding (Fig. 2). There are two identified receptors for OX/HCRT, the G-protein coupled receptors, OX Receptor-1 (OXR-1) and OX receptor-2 (OXR-2). These receptors are expressed throughout the brain, including the VTA, where they are typically coupled to Gq proteins [95–97]. Intriguingly, OX/HCRT differentially regulates firing of projection-specified populations of VTA DA neurons, and notably activates those projecting to the NAc but not those projecting to the amygdala [73]. This difference could be due, in part, to differential expression of OX/HCRT receptors on VTA neurons projecting to the NAc vs. the amygdala, though this has yet to be shown definitively. Going forward, it will be instructive to determine if OX/HCRT receptor expression in the VTA can be used to distinguish DA subpopulations and their functions.

2.2. Neurotensin

Many neurons expressing the neuropeptide neurotensin (Nts) provide input to the VTA, with the largest populations originating from the medial preoptic area, NAc and the LHA [98]. Interestingly, at least some LHA Nts-expressing neurons are regulated by leptin;

approximately 30% of Nts neurons co-express the long form of the leptin receptor (LepRb) [66]. Given that leptin itself suppresses feeding, leptin acting on LHA Nts-containing neurons might promote anorexic effects, perhaps via Nts itself. While this has yet to explored explicitly, activating LHA Nts-expressing neurons does increase Nts release into the VTA [99,100], and pharmacologic Nts treatment into the VTA has been shown to reduce feeding [101,102]. Moreover, pharmacologic administration of Nts in the VTA potentiates excitatory synaptic transmission and increases the firing rate of DA neurons, which in turn promotes the release of DA in the NAc [103,104]. This leads to feeding restriction, increased locomotor activity and ultimately weight loss in obese rodents [105–107]. In combination, these data confirm that Nts modulates VTA DA neurons and can exert anorectic effects. It is notable that both Nts and OX/HCRT are reported to activate VTA DA neurons, but exert opposing effects on feeding. One possible hypothesis to explain this conundrum is that these neuropeptides might engage separate subsets of VTA DA neurons that differentially modify feeding. If true, expression of receptors for OX/HCRT vs. Nts could be a means of discerning which VTA neurons respond to these neuropeptides, and whether they comprise separate subpopulations. This hypothesis has yet to be directly explored. However, comparing the distributions of OX/HCRT and Nts receptors in the VTA will be vital to assess how each of these neuropeptides can promote activation of VTA DA neurons but yield completely different control of behavior.

The VTA can directly respond to Nts since it contains both of the signaling forms of the neurotensin receptors, neurotensin receptor -1 and -2 (NtsR1 and NtsR2) [55,108,109]. Intriguingly, Nts action via NtsR2 is not a direct modulator of VTA DA neurons, since NtsR2 is almost exclusively expressed in VTA astrocytes [110]. By contrast, NtsR1 is the predominant receptor isoform expressed by VTA DA neurons [55], and is vital for Nts-mediated DA release into the NAc [100]. Moreover, only a subset of VTA DA neurons express NtsR1, and these neurons preferentially project to the NAc and not to the PFC [55]. Thus, NtsR1 represents a molecular marker of primarily mesolimbic, not mesocortical VTA DA neurons, but the specific role of these VTA NtsR1 neurons remains incompletely understood. Loss of NtsR1 increases feeding but also further elevates energy expenditure (primarily through an increase in physical activity), and this energy imbalance promotes leanness [110]. Furthermore, intact NtsR1 expression is required for LHA Nts-LepRb neurons to restrain feeding, indicating the functional integration of leptin and Nts/NtsR-1 action [71]. At least some of these feeding restraint effects are mediated via the LHA Nts neurons that project densely to the VTA [99,100], and depends on $NtsR1^{112}$. Taken together, these data indicate that Nts input to the VTA can promote weight loss behaviors, at least in part, due to regulation of NtsR1-expressing DA neurons. It yet remains unclear how the VTA NtsR1 neurons specifically mediate anorectic signals, or if they are sufficient to promote weight loss behaviors, which warrants examination in the future.

2.3. Galanin

LHA galanin neurons partially overlap with LepRb-expressing neurons or Nts neurons [111–114]. Since some LepRb and Nts neurons project to the VTA it was long reasoned that these neurons release the neuropeptide galanin into the VTA as well. Intriguingly, recent evidence suggests that LHA galanin neurons are one of the few LHA populations that do not engage the VTA directly, and instead project locally within the LHA to regulate OX/HCRT neurons that express the galanin receptor. LHA galanin neurons do impact feeding via this local circuit, specifically modifying nutrient preference (sucrose > fat) [112]. Mice that lack the LepRb from their LHA galanin expressing neurons show an increase in OX/HCRT neuronal activation [112], which suggests that LHA galanin-LepRb expressing neurons inhibit OX/HCRT neurons under baseline conditions. Importantly, it remains possible that LHA galanin neurons can indirectly impact activation of VTA DA neurons via modulating OX/HCRT neurons that project to the VTA. On the other hand, activation of LHA Nts neurons, some of which co-express galanin [113], can modestly suppress feeding [99]. Since many LHA Nts neurons project to the VTA [98], these data suggest that there must be a population of Nts-only neurons in the LHA that project to the VTA, in addition to an LHA subset that co-expresses Nts and galanin and projects locally. It is therefore possible that the LHA Nts-only neurons that project to the VTA mediate Nts-mediated anorectic actions via the NtsR1 expressed on VTA NtsR1-DA neurons.

2.4. Melanin-concentrating hormone

Melanin-concentrating hormone (MCH) is a defining neuropeptide of the LHA, as its expression is restricted to this brain region. While some studies have described MCH fibers and mRNA from MCH receptors in the VTA, others show low to no expression of MCH receptors in the VTA [95,115–118]. Although the LHA as a whole provides dense input to the VTA, the widely accepted view is that MCH neurons are a notable exception, and do not significantly project to or directly regulate the VTA [116]. Nevertheless, MCH has well-established connections with other sites that contribute to changing behavior (cerebral cortex, LHA, amygdala, and NAc [119–122]), where it has been implicated in orexigenic intake of foods, as well as in cocaine- and amphetamine-induced reward and reward learning [123,124]. Thus, while MCH is an LHA neuropeptide with important roles in modulating feeding, it does not exert these actions via direct engagement of VTA DA neurons.

2.5. Corticotropin releasing factor

Corticotropin releasing factor (CRF) is widely expressed throughout the brain, including regions of the forebrain, the VTA and within a subset of LHA neurons that are activated by dehydration anorexia [125–127]. In addition, pharmacologic and endogenous CRF suppress feeding in both lean and obese mice [128]. CRF signals through the CRF receptor-1 and -2 (CRFR1, CRFR2). Not much is known about CRFR2 signaling, but the CRF/CRFR1 system has been repeatedly associated with stress and addiction [129,130]. Accordingly, CRFR1 is expressed in DA neurons of the VTA and the adjacent substantia nigra pars compacta (SNc) [131]. A recent study revealed that VTA CRFR1 expressing DA neurons primarily project to the NAc core, rather than the NAc shell, and their activation is important for associating stimuli and behaviors more so than augmenting the wanting of those stimuli [43]. While feeding was not specifically studied, it may be that VTA CRFR1 neurons play a role in learned feeding behaviors, and this will merit further attention. Going forward it will be important to investigate if LHA-derived CRF signaling modulates feeding via the VTA CRFR1 neurons, and what the role of the CRF neuropeptide is in this process vs. other signals released from LHA CRF neurons.

2.6. Summary and implications

VTA DA neurons are now recognized to be heterogenous via multiple criteria, and this opens the door to investigating whether subsets of VTA DA neurons may mediate different aspects of feeding behavior. Given the significant diversity in the types of signals that access the VTA, it seems possible that VTA DA neurons may accordingly tune feeding behavior in response to them. Going forward, “mapping” the populations of VTA DA neurons via their neuropeptide receptor expression could prove instructive, as it might identify subsets that contribute to orexigenic or feeding restraint behaviors. Given that LHA neurons project to, and act in concert with VTA DA neurons to modify behavior, assessing VTA DA neurons that express receptors for LHA-released signals might suggest which neurons modulate feeding, and how they do so. However, it is likely that subsets of VTA DA neurons will not express a single neuropeptide receptor subtype, but in fact, a

suite of neuropeptide receptors. Such a system could enable VTA DA neurons to flexibly respond to different cues and from different inputs, not all of which may be active at the same time. Thus, it remains possible that there could be subsets of DA neurons that primarily mediate orexigenic responses vs. those that constrain feeding or other rewards and mediate these responses via a collection of expressed neuropeptide receptors. There remains much to learn, however, regarding the mechanisms by which neuropeptides modulate the VTA and feeding. For example, neuropeptides from the LHA (and elsewhere) may change the balance of tonic vs. burst-firing of DA neurons, the latter of which is associated with changing goal-mediated behavior. Thus, in the future it will be important to characterize how specific neuropeptides, or combinations of them, impact the firing pattern of DA neurons. It is also likely that neuropeptides may modulate other VTA neuronal populations (e.g. GABA or glutamate containing neurons) or glial populations, which can in turn indirectly modify the activity of local DA neurons or other external targets. While we have focused on how LHA neuropeptides can directly engage DA neurons that express their cognate receptors, neuropeptide modulation of other VTA cells could have powerful effects on feeding behavior and warrant further study. In any case, going forward it will be important to determine if neuropeptide receptors can be used to molecularly distinguish the projection and functionally specified populations of DA neurons, or other VTA cell types that impact feeding. These studies would not only advance understanding of the basic biology regulating energy balance but could also suggest how to design molecular-based tools to dissect the function of specific VTA cell subsets.

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