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Melanin-concentrating hormone and food intake control: sites of action, peptide interactions, and appetition

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Abstract

Given the increased prevalence of obesity and its associated comorbidities, understanding the mechanisms through which the brain regulates energy balance is of critical importance. The neuropeptide melanin-concentrating hormone (MCH) is produced in the lateral hypothalamic area and the adjacent incerto-hypothalamic area and promotes both food intake and energy conservation, overall contributing to body weight gain. Decades of research into this system has provided insight into the neural pathways and mechanisms (behavioral and neurobiological) through which MCH stimulates food intake. Recent technological advancements that allow for selective manipulation of MCH neuron activity have elucidated novel mechanisms of action for the hyperphagic effects of MCH, implicating neural “volume” transmission in the cerebrospinal fluid and sex-specific effects of MCH on food intake control as understudied areas for future investigation. Highlighted here are historical and recent findings that illuminate the neurobiological mechanisms through which MCH promotes food intake, including the identification of various specific neural signaling pathways and interactions with other peptide systems. We conclude with a framework that the hyperphagic effects of MCH signaling are predominantly mediated through enhancement of an “appetition” process in which early postoral prandial signals promote further caloric consumption.

1. Introduction:

The brain regulates energy balance, in part, via responses to peripheral-derived interoceptive physiological cues that acutely alter energy intake and expenditure such that body weight remains relatively stable [1]. However, in an environment where energy dense and highly

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palatable foods are readily available and require little effort to obtain, obesity (42.4% of US adults in 2018) and severe obesity (9.2% of US adults in 2018) rates are at an all-time high [2], suggesting a bias toward energy conservation and surplus under these conditions. Furthermore, evidence suggests that appetite control and energy expenditure function to defend a higher body weight in previously obese people, thereby thwarting behavioral attempts at sustaining weight loss [3–7]. Given the challenges to weight loss imparted by the inherent physiological and behavioral bias towards energy conservation, it is critical to understand the neurological systems that promote positive energy balance. The melanin-concentrating hormone (MCH) system is one such system, as it has been shown to impact both energy intake and energy expenditure, overall promoting positive energy balance [8–10]. The purpose of this review is to summarize the current understanding of the MCH system in energy balance control, with an emphasis on highlighting recent findings that inform about neural sites of action and neurochemical mechanisms through which MCH stimulates excessive caloric intake. Collective findings described herein support a framework in which MCH contributes to postoral “appetition” to stimulate caloric consumption.

2. MCH: energy balance and metabolism

The chemical and biological characteristics of MCH were first described by Kawauchi and colleagues in the pituitary of salmon in 1983 [11]. Mammalian MCH is a cyclic, nineteen amino acid neuropeptide that is almost exclusively produced in the lateral hypothalamic area (LHA) and the incerto-hypothalamic area (IHy) in the brain [12]. However, while immunoreactivity for MCH has primarily been described in the LHA and IHy, pre-pro-MCH RNA, the gene precursor for MCH and two additional neuropeptides (Neuropeptide EI and Neuropeptide GE), has been identified in at least 9 additional regions (reviewed in [12]). MCH neurons have extensive projections throughout the neuraxis, and its G-protein coupled MCH receptor, melanin-concentrating hormone 1 receptor (MCH1R), is expressed throughout the brain [13, 14]. Acting through MCH1R [15], MCH promotes overall energy conservation and/or surplus by increasing food intake and/or reducing energy expenditure [16–18]. Extensive evidence, including from a seminal study in 1996 [8], shows that elevating MCH generally in the brain, either through ventricular administration (ICV) [19–22] or transgenic MCH overexpression [16] increases food intake, while ICV injection of MCH1R antagonists reduce food intake [10]. Moreover, these increases occur regardless of the food’s palatability and/or obesity-promoting effects [23]. The acute hyperphagic effects of a single ICV MCH injection are extinguished after 24hr, while chronic infusion increases food intake and body weight over time [24]. Both male and female mice lacking the MCH gene are leaner than wild-type controls, which is attributed to hypophagia and altered metabolic rate [17]. Similarly, ablation of MCH neurons reduces age-associated weight gain [25] and is further associated with leanness in older mice [26]. While chemogenetic DREADDs-mediated activation of MCH neurons increases food intake in rats [27], chemogenetic MCH neuron activation in transgenic mice has no effect on food intake [28], suggesting possible species differences with regards to the hyperphagic effects of MCH neuron activation.

While manipulations of MCH or the MCH neurons impact both food intake and energy expenditure, thus implicating MCH as a signal to favor positive energy balance, the impact

of MCH1R signaling on energy balance is less straight forward. Both central [10] and peripheral [29] antagonism of MCH1R decreases food intake through a reduction in meal size. However, deletion of the MCH1R reveals a more complex landscape. Transgenic MCH1R−/− mice are smaller than their wild-type counterparts, despite increases in chow intake [30, 31]. Additionally, male and female MCH1R−/− mice fed a high fat diet are resistant to diet-induced obesity [32]. Taken together, evidence supports that while MCH and MCH1R signaling increase food intake and reduce energy expenditure, complete loss of MCH1R increases energy expenditure without coupled compensatory effects on food intake.

The role of MCH in body weight regulation has prompted a search for pharmacological antagonists that can be used in humans to treat obesity [33–40]. However, it is important to note that humans express a second MCH receptor, melanin-concentrating hormone 2 receptor (MCH2R), which is absent in rodents [41–46]. MCH2R is largely co-expressed with MCH1R [41], yet its physiological function has not been identified. While there are presently no viable animal models for the investigation of endogenous MCH2R effects on energy balance, Chee and colleagues showed that overexpression of human MCH2R in transgenic mice prevents diet-induced obesity by reducing food intake, suggesting possible similarities between the two receptor variants with regard to energy balance outcomes [47].

To better understand the mechanisms through which MCH alters energy balance, it is important to note that MCH interacts with post prandial signals that also impact energy balance. For example, MCH mRNA is significantly increased after peripheral insulin treatment [48], and a subset of MCH neurons are directly excited by insulin [28]. However, overexpression of MCH leads to insulin resistance [16]. In diet-induced obese mice (but not lean mice), inactivation of insulin receptors on MCH neurons increases insulin sensitivity and diminishes hepatic gluconeogenesis [28]. MCH neurons are also depolarized by extracellular, physiologically-relevant concentrations of glucose in a dose-dependent manner [49], and these neurons, once activated by glucose, work to regulate blood glucose levels [50]. This effect is exemplified by impaired glucose tolerance following disruption of MCH neuron glucose signaling [50]. The influence of MCH neurons on glucose regulation may be mediated, in part, by glutamate as loss of glutamatergic signaling from MCH neurons improved glucose tolerance in mice, whereas knockout of the MCH peptide had no effect [51]. As one might hypothesize from these findings, endogenous levels of MCH [52, 53] and MCH1R mRNA [54] are elevated in the brains of fasted rodents. Interestingly, MCH−/− mice observed into maturity have improved blood glucose tolerance and insulin sensitivity [25], yet an absence of MCH does not alter post-prandial circulating levels of glucose or insulin [17, 50]. These data demonstrate the complex nature of the MCH system and metabolic parameters, such that elevated MCH signaling leads to insulin resistance and possibly elevated blood glucose, whereas MCH-deficient animals exhibit increased insulin sensitivity and improved glucose tolerance in adulthood. These data also highlight that MCH signaling promotes a positive energy balance and the need for more research into MCH system regulation of glucose tolerance and insulin sensitivity.

The MCH system may promote food intake, in part, by enhancing the reinforcing properties of postingestive cues. For example, intraperitoneal injection of MCH1R antagonist attenuated self-administration of a caloric, sweetened solution (sucrose), but not a non-

caloric, sweetened solution (saccharin) [55]. Furthermore, optogenetic stimulation of MCH neurons paired to a non-caloric sweetener alters the natural preference of a caloric sweetener over a non-caloric sweetener, sucralose [56]. Additionally, sweet-blind *Trpm5*$^{-/-}$ mice show a preference for sucrose over sucralose, however when MCH neurons are ablated by diphtheria toxin, this preference is abolished [56]. Interestingly, loss of glutamatergic signaling from MCH neurons conferred a similar effect: no preference for sucrose over sucralose [51]. Comparing MCH1R−/− mice to wild-type mice, Sclafani and colleagues demonstrated that MCH1R is not essential for postingestive reinforcement [57], further speaking to the divergence seen when comparing manipulations of MCH neurons and complete deletion of MCH1R. These discrepancies may due to the under-appreciated role of glutamate signaling from MCH neurons and/or due to the widespread possible neural sites of action for MCH (based on extensive MCH neuron projections and expression of MCH1R throughout the neuraxis) [14], highlighting the importance of understanding the site-specific actions of central MCH signaling.

3. Sites of action for MCH effects on food intake:

In contrast to lateral and third ventricle injections of MCH [58] that access both the forebrain and the hindbrain sites, Baird et al. reported that fourth ventricle injections (which are restricted to the hindbrain) of MCH are not sufficient to increase meal size, meal frequency, nor meal duration [59], suggesting that the site(s) of action for MCH feeding effects are most likely entirely in the forebrain. Thus, the following section focuses on forebrain sites of action where MCH signaling has been reported to modulate feeding behavior. Further, we note that sex differences in the MCH system have not been extensively studied (but see Estrogen section 5, below), and thus where male and/or female data are available in the context of this discussion, it has been noted accordingly.

Hypothalamic subregions:

MCH neurons project to several regions within the hypothalamus, including the arcuate nucleus (ARH), the paraventricular (PVH), the supraoptic nucleus (SO), the ventromedial nucleus (VMH), the dorsomedial nucleus (DMH), the supramammillary nucleus (SUM), the median eminence (ME), and to other neurons within the LHA and IHy [14, 60]. Surprisingly, there is a paucity of behavioral data relevant to the hypothalamic MCH1R system, although the electrophysiological properties of such have been reviewed [61]. *In vitro* data reveal that when applied to medial basal hypothalamic explants, MCH stimulates the release of neuropeptide Y (NPY) and agouti-related peptide (AgRP), while inhibiting the release of cocaine- and amphetamine-regulated transcript (CART) and alpha-melanocyte-stimulating hormone (αMSH) [62]. At the behavioral level, MCH intranuclear injections into either the medial preoptic area (MPN), VMH, or LHA did not elicit an increase in chow intake in rats, although a trend toward significance was noted following MCH injection to the SO and the anterior hypothalamic area [62]. However, injection of MCH into the PVH significantly elevates chow intake [19, 62], as does MCH injection to the DMH or ARH, with more potent effects observed following ARH application [62].

MCH neurons also send dense projections to the ME, and these projections have been shown to modulate the blood-brain barrier (BBB) [63]. This modulation likely has consequences on energy balance, as it was shown that optogenetic and chemogenetic activation of MCH neurons enhances the permeability of the ME barrier, and promotes leptin signaling in the ARH [63]. This modulation of the BBB by MCH neurons is not acting through MCH directly, but rather through vascular endothelial growth factor A (VEGFA) produced by MCH neurons [63]. Whether MCH is also significant to the central responses to circulatory peripheral cues remains to be determined. Notably, the MCH system has been implicated in the downstream effects of other feeding-relevant neuromodulators, a topic discussed in more detail in sections 4 and 5.

Nucleus accumbens:

The nucleus accumbens (ACB) is well known for its role in reward-motivated behaviors, including food intake [64–66], and has two distinct regions: the shell (ACBsh) and the core (ACBc) [67]. MCH neurons densely project to the ACB, with a greater concentration in the ACBsh than in the ACBc [14]. Similarly, MCH1R expression is present throughout the ACB, with the highest Density of expression in the ACBsh [15, 68].

The ACBsh has an established role in feeding, in part, via inhibitory neurotransmitter signaling. For example, GABA agonists injected into the ACBsh elevate food intake [66], while similar doses of GABA receptor agonists to the ACBc (core) have no effect on consumption [66]. Expanding on these reports, Urstadt and colleagues showed that either GABA receptor agonist, NMDA receptor antagonist, or AMPA receptor antagonist injected into the ACBsh decreases latency to feed and increases both meal duration and frequency [69]. As these results relate to MCH, Haemmerle and colleagues provided evidence that MCH projections modulate GABAergic medium spiny neurons (MSNs) of the ACBsh [70]. These effects may be relevant to feeding, as Georgescu et al. demonstrated that bilateral injections of MCH into the ACBsh at the beginning of the dark cycle potently increased intake of regular chow [64]. Furthermore, MCH injections to the ACBsh 4h into the dark cycle in sated animals elevated chow intake to a magnitude comparable to injections at the beginning of the dark cycle [64]. Further supporting the endogenous relevance of ACBsh MCH signaling in normal food intake, bilateral injections of an MCH1R antagonist to the ACBsh at the beginning of the dark cycle significantly reduced chow intake [64]. Similarly, MCH1R agonist injected to the ACBsh has been shown to elevate chow consumption [71], and in Pmch −/− mice that exhibited diminished meal size, MCH ACBsh injections elevated food intake to control levels [72]. Our recent findings further show the orexigenic effects of MCH ACBsh signaling are robust across multiple parameters, including different foods (sucrose, chow), light vs. dark cycle analyses, and pharmacological vs. chemogenetic approaches [73]. While these findings collectively clearly identify a role for MCH ACBsh signaling in food intake control, MCH bilaterally injected into the ACBsh had no effect on food seeking behaviors in the conditioned place preference model [74], suggesting that the effect of MCH in the ACBsh is more likely based on enhancing consummatory vs. appetitive behavior.

Hippocampus:

MCH neurons in the LHA/IHy send dense projections to the ventral subregion of the hippocampus (HPCv) [14, 23], and HPCv neurons robustly express MCH1R [15, 23]. The HPCv also contains a multitude of receptors responsive to meal-associated interoceptive cues, and has been shown to play a role in learned appetitive behavior, meal size control, and motivated responding for food (for review see [75]), as well as impulsive responses for food reinforcement [76]. Our group recently investigated whether HPCv MCH signaling affects food intake and impulsivity for palatable food [23]. ICV MCH injection, MCH injection into the HPCv CA1 region, and chemogenetic activation of a subset of MCH neurons projecting to the HPCv CA1 region each elevated impulsive responding for palatable food [23]. Moreover, neither HPCv-targeted manipulation influenced home cage food intake, suggesting a selective effect of HPCv MCH signaling on appetitive impulsive behavior. Paradoxically, MCH receptor knockdown in the HPCv also increased palatable food-directed impulsivity [23], suggesting that the system may be sensitive to fluctuations in either direction with regards to HPCv MCH signaling tone and impulse control.

In the dorsal subregion of the hippocampus (HPCd), the CA3 region has a high expression of MCH1R [15] and considerable density of MCH immunoreactive axon terminals [14]. Using a model of pharmacological blockade of HPCd CA3 MCH signaling, Sita and colleagues concluded that HPCd MCH signaling does not influence food seeking behavior or spatial memory for food location in a food-seeking working memory task, yet HPCd MCH signaling may be necessary for switching from the searching to the consummatory phase of ingestion [77]. These findings highlight the need to future investigation into the role of HPCd MCH in modulating food intake and food-directed behaviors.

Cerebrospinal fluid:

While ICV injections are widely accepted as a technique to generally upregulate or block a specific compound in the central nervous system, the cerebrospinal fluid (CSF) itself has long been postulated to act as a physiological conduit for delivery of neural signaling molecules [78]. “Volume transmission” was initially proposed as a humoral pathway by which neural compounds can communicate with distant regions of the central nervous system [78]. Our group recently showed that MCH neurons stimulate home cage feeding behavior via CSF-mediated volume transmission [79]. Approximately one-third of MCH-producing neurons terminate at the ependymal cells lining the cerebral ventricles, and chemogenetic activation of these neurons yields an acute and robust increase in CSF MCH levels [79]. Behaviorally, at the beginning of the dark cycle prior to the first feeding bout, we observed an endogenous increase in CSF MCH levels, and antibody-based sequestration of MCH in the CSF to selectively remove endogenous CSF MCH transmission resulted in a reduction in food intake [79]. These findings bring attention to several inquiries for future investigation, such as the target(s) of CSF MCH signaling through which MCH is being transmitted by the CSF [79]. Though technically challenging, further investigation of this understudied MCH CSF volume transmission pathway is warranted.

4. Interactions with feeding-related peptide systems:

Energy balance regulation involves a multitude of neuropeptide systems in the brain that interact both with each other, and with physiological cues related to energy status to modulate food intake [80, 81]. Indeed, the MCH system interacts with a various interoceptive cues as well as other neuromodulatory systems to regulate food intake. Below we highlight several known interactions between MCH and other peptide systems of relevance to food intake and energy balance.

Leptin:

Leptin is secreted from adipocytes to attenuate food intake and increase energy expenditure [82, 83], whereas MCH works to do the opposite: promote overall positive energy balance [8]. Several lines of evidence suggest the MCH system may be a downstream effector of leptin signaling in the regulation of body weight. For example, three days of ICV leptin administration significantly reduces body weight, food intake, and MCH mRNA in ad libitum fed rats, while a similar reduction in MCH expression was not observed in pair-fed controls [83]. Interestingly, others have shown that compared to wild type animals, ob/ob mice with a leptin deficiency have increased levels of MCH mRNA [53] and MCH1R mRNA expression [54], and leptin treatment to these leptin-deficient mice blunted the increases observed in MCH and MCH1R expression [53, 54]. In congruency, obese Zucker rats, another model of leptin deficiency, show significantly increased hypothalamic prepro-MCH mRNA, but contrastingly present with significantly decreased hypothalamic MCH1R mRNA [84]. Together these data suggest that a lack of leptin signaling may upregulate the MCH system in the brain and that in these cases replenishing leptin signaling reduces MCH expression.

Interestingly, mice lacking both MCH1R and leptin have similar food intake and body weight compared with mice lacking leptin alone. However, the metabolic profile of MCH1R knockout ob/ob mice is quite different from ob/ob mice with a functioning MCH system [85]. For example, MCH1R knockout ob/ob mice are leaner, have higher locomotor activity, and have improved glucose metabolism [85]. Taken together these data suggest that the MCH system is required for some of leptin's metabolic effects, but likely not for leptin's anorexigenic actions.

Recent findings suggest that the MCH neurons themselves may regulate leptin sensitivity in the brain by modulating the capacity for leptin to cross the BBB. Namely, optogenetic and chemogenetic activation of MCH neurons increases fenestration of the capillaries surrounding the ME [63]. This increased fenestration provides an entry point for leptin to cross the BBB and take action in the ARH, thereby suppressing feeding behavior [63]. While this study showed that it is activation of MCH neurons and not the MCH peptide itself that mediates the BBB modulatory effects, prior data have shown that activating MCH neurons also increases food intake via an MCH1R mediated mechanism [79], and thus these findings bring into question whether there may be some mechanism whereby activating MCH neurons both increases food intake and allows for enhanced leptin-mediated satiation signaling.

Orexin:

Similar to the MCH neurons, the orexin (also known as hypocretin [O/H]) neurons, are unique to the LHA [86]. There exists two forms of O/H: orexin A (hypocretin 1) and orexin B (hypocretin 2), along with two receptor subtypes: orexin A/hypocretin 1 receptor and orexin B/hypocretin 2 receptor [86]. O/H neurons have been shown to play a critical role in arousal, cognition, and the reward system [87]. While the role of O/H in affecting overall levels of food intake is controversial [88], O/H has been extensively shown to increase food seeking behavior [89–91], as well as the intake of palatable foods [89, 92]. Additionally, O/H and MCH neurons innervate many of the same brain regions [93]. It has been proposed that while O/H is primarily responsible for food seeking behaviors, MCH neurons affect intake once feeding has begun, contributing to ongoing consumption [9](see Section 5 below for further discussion on this interactions).

The O/H and MCH neurons are anatomically connected [94, 95], and each expresses the other's receptor [96], and these neuron populations affect, albeit in slightly different ways, food intake control [9]. In vitro application of exogenous O/H to MCH cells is excitatory [97], whereas optogenetically stimulating O/H neurons promotes a sharp suppression of MCH neuronal activity that is blocked by GABAA receptor antagonist [95]. Interestingly, blockade of O/H receptors significantly diminished the GABAergic tone in the LHA, suggesting that GABAergic interneurons expressing O/H receptors may mediate the impact O/H has on MCH neurons [95]. As reported earlier, application of physiologically-relevant levels of glucose excites MCH neurons, but inhibits O/H neurons [49]. Moreover, during feeding O/H cell activity in freely feeding mice was measured by fiber photometry, and Gonzalez et al. reported that within a second of meal initiation, O/H activity was diminished, immediately ramping back up at the finish of the meal [98]. Future studies in the area may focus on MCH neuron activity in freely feeding mice to compare to the activity of both cell types.

Arcuate hypothalamic peptide systems (NPY, AgRP, POMC: (a-MSH)):

The ARH plays an important role in food intake and overall energy balance [99]. Although not all exclusive to the ARH, peptidergic neurons of the ARH, some mutually expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP), and others expressing alpha-melanocyte-stimulating hormone (αMSH), innervate LHA MCH neurons [100]. As aforementioned, application of MCH to hypothalamic explants stimulated the release of neuropeptide Y (NPY) and agouti-related peptide (AgRP), while inhibiting the release of cocaine-and amphetamine-regulated transcript (CART) and alpha-melanocyte-stimulating-hormone (αMSH) [62].

The *Pomc* gene codes for a variety of peptides, including the anorectic peptide αMSH which is an agonist for the melanocortin receptor types 3 and 4 [101]. Melanocortin receptor types 3 and 4 minimally colocalize with MCH-producing neurons [102], however, 19% of POMC neurons express MCH1R [103]. A functional interaction between MCH and melanocortin signaling is supported by data showing that ICV injection of αMSH significantly attenuates ICV MCH-induced hyperphagia [104], and, likewise, MCH blocks the anorectic actions of αMSH [105]. Further, ICV MCH administration significantly attenuates hypothalamic

POMC protein levels, leaving other feeding-related peptides unaltered [103]. In mice lacking MCH, *Pomc* is under-expressed [17, 106], and mice lacking the *Pomc* gene display increased expression of hypothalamic MCH mRNA while expression of several other feeding-related peptides remained unaltered [107]. Along with elevated levels of hypothalamic MCH gene expression, *Pomc* −/− mice were significantly heavier at 8 weeks compared to their wild-type counterparts and were more susceptible to high fat diet-induced obesity [107]. Finally, Al-Massadi and colleagues found that chemogenetic inhibition of sirtuin-1, a deacetylase activated by caloric restriction, in POMC neurons attenuated the effects of chronic ICV MCH administration on weight gain, hyperphagia, and adiposity [103]. These findings collectively suggest that the expression and action of POMC and MCH are intimately intertwined, in that the MCH system requires POMC neurons to confer its effect on energy balance.

NPY is an extremely potent orexigenic peptide [108] and NPY Y1 [109] and Y5 [102] receptors are expressed in the LHA MCH neurons [110]. Interestingly, NPY receptor antagonists significantly block the orexigenic effect of ICV MCH injection, suggesting that the NPY Y1 and Y5 receptors are mediators of MCH effects on food intake [111]. NPY has been shown to depress MCH neuron activity *in vitro* [97], and this has been speculated to be a part of a negative feedback loop in which MCH activity activates NPY neurons that then reduce MCH activity [61]. This putative MCH-NPY feedback loop framework is consistent with MCH involvement in “appetition”, a concept discussed at length in our conclusion.

The vast majority, but not all, of NPY neurons co-express AgRP [112, 113]. Although administration of ICV AgRP and overexpression of AgRP enhances transcription of MCH mRNA [114], ICV administration of MCH [20], deletion of MCH, or deletion of MCH1R has no effect on expression of AgRP [17, 31]. More research is necessary to further elucidate the possible negative feedback loop involving MCH and NPY and what role, if any, AgRP plays in this purported feedback loop.

Dopamine:

Feeding behavior is driven by both homeostatic regulatory signals that aim to maintain an animal’s energy balance and by incentive- and hedonic-based signals that contribute to the pleasurable aspects of eating. Incentive motivation for food and other reinforcers is associated with the neurotransmitter, dopamine (DA), and two of its receptors, D1-like dopamine receptor (D1R) and D2-like dopamine receptor (D2R). The predominant neural pathway through which DA modulates incentive processing for food reward and food-associated cues involves signalling from DA-producing neurons in the ventral tegmental area (VTA) to DA receptors in the ventral striatum, especially the ACB [115].

As briefly discussed above, the ACB, in particular the ACBsh subregion, expresses high levels of MCH1R [116], and ACBsh neurons are densely innervated by MCH neurons [14], indicating the plausibility that MCH ACBsh signaling is based on a monosynaptic connection from LHA and/or IHy MCH neurons. Evidence suggests that MCH and dopaminergic systems interact in the ACBsh, however, the mechanisms behind how these systems interact to influence behavioral outcomes remain to be fully determined. In the mouse ACBsh, MCH1R is co-expressed with D1R and D2R, and ACBsh neuronal activity

increases in the presence of MCH combined with both D1R and D2R agonists, but not following application of only one of the agonists [117]. Interestingly, in MCH1R −/− mice, who have elevated levels of locomotor activity and show enhanced sensitivity to activity-promoting effects of D1R agonists, there is an up-regulation of D1R and D2R receptor expression and DA binding in the ACBsh [118]. This hyperactivity and dysregulation of dopamine action is replicated when the MCH receptor is selectively silenced in the ACBsh [119]. Furthermore, administration of MCH in the ACB of mice explants blocks D1R induced phosphorylation of the AMPA glutamate receptor subunit Glu1R [64], supporting an inhibitory effect of MCH on D1R signaling. Similarly, D1R and D2R activation in hypothalamic mouse brain sections leads to a decrease in excitability of MCH neurons [120], suggesting a putative negative feedback loop. Importantly, these effects were both dose- and receptor-dependent. For example, at a low dopamine dose, D1R are activated, resulting in more GABA release onto the MCH neurons. On the other hand, at a high DA dose D2R are activated, which inhibit GABA release, yet also activates a noradrenergic receptor which inhibits MCH neurons through GIRK channels [120].

Activation of MCH neurons in mice alters ingestive behavior, potentially via augmented striatal DA release. For example, Domingos and colleagues showed that optogenetic activation of MCH neurons during intake of nonnutritive sucralose increases DA release in the striatum, and inverts the normal preference of sucrose vs. sucralose [56]. Furthermore, the same study revealed that ablation of MCH neurons reduces striatal DA release upon sucrose intake. These effects may be based on post-ingestive (and not orosensory) effects, as sweet-blind mice show a conditioned preference for sucrose vs. sucralose, yet this preference is blocked with MCH neuron ablation [56]. Collectively, these results indicate a complex, possibly complementary, interaction between DA and MCH on neural responses that is influenced by DA receptor type and dose responses. Yet unknown is how central MCH signaling influences ventral striatal DA signaling in response to palatable food and food-associated stimuli.

Opioid peptides:

The opioid system, while most commonly investigated in the context of analgesia and drugs of abuse, also has a critical role in regulating feeding behavior. For example, agonizing or antagonizing each of the opioid receptors (**κ**-OR, μ-OR and ***δ***-OR) potently increases and decreases food intake, respectively [121]. Furthermore, central opioid signaling stimulates positive/appetitive hedonic orofacial evaluation of tastants, which is measured in rodents by the taste reactivity test that categorizes responses to a given taste stimuli into positive or negative hedonic orofacial motor responses by observing standardized oral and body responses to orally delivered stimuli [122, 123]. Opioid signaling, specifically through μ-OR, induces a hyperphagic effect and enhanced positive orofacial taste reactivity responses for taste stimuli, particularly for foods that have higher hedonic values (i.e., are more preferred) for that animal [124–127]. ACBsh neurons express a high density of both MCH1R [116] and opioid receptors [128], indicating a possible connection between the two systems in mediating hedonic properties of food consumption.

Lopez and colleagues found that pharmacologically inhibiting any one of the opioid receptors (κ-OR, μ-OR and δ-OR) via ICV administration of specific opioid receptor antagonists prior to ICV infusions of MCH prevented MCH-induced hyperphagia in rats [129]. Further, using the taste reactivity test they found that either lateral ventricle (LV) or direct ACBsh administration of MCH increased the positive hedonic orosensory response to the sucrose solution. However, blocking any of the three opioids receptors via ICV infusion of specific opioid receptor antagonists reduced the positive hedonic orosensory response [129]. This study indicates a complementary connection between the MCH and opioid system, where the opioid system mediates the orexigenic and hedonic orosensory effects of MCH in the ACBsh. It is important to note that during the taste reactivity test the opioid receptor antagonists were only administered in the LV and not in the ACBsh, and thus this interaction may be indirect and involve other brain regions.

In addition to the evaluation of effects on orosensory hedonic responses, other studies have elucidated a functional interaction between each of the opioid receptors and MCH with regards to caloric intake. For example, ICV infusion of κ-OR antagonist in mice has the same effect as a general opioid antagonist in attenuating MCH-induced feeding [130]. Related, MCH neurons have significantly higher colocalization with κ-OR compared to μ-OR and δ-OR [102]. Thus, the κ-OR may have a stronger general influence on the MCH system compared to other opioid receptors. On the other hand, Clegg and colleagues showed that opioid receptor antagonists had no effect on MCH-mediated hyperphagia [131]. However, these studies used naloxone, an opioid receptor antagonist that binds to all the opioid receptors with lower affinity compared to opioid receptor antagonists that are specific to each of the opioid receptors. It is possible that there is a hierarchy of opioid receptors in regard to their interactions with the MCH system, as suggested by the results of Romero-Pico and colleagues [130]. Collectively, however, it appears that MCH and opioid signaling have common effects on food intake and hedonic orofacial motor responses.

Estrogen:

Sex-specific effects on feeding behavior may involve differences in female reproductive hormone signaling pathways, such as estrogen. Estrogen levels cyclically vary in females, and qualitatively differ from males. Generally speaking, estrogen has anorexigenic effects [132], suggesting that eating patterns may naturally vary in cycling females. When estrogen receptor alpha (ERα) is knocked down, female mice are hyperphagic and obese with elevated adipose tissue [133]. ERα has been shown to be highly expressed in the LHA [134], and thus, estrogen may be a critical variable acting in a sex-dependent manner to mediate MCH-induced feeding effects.

A connection between MCH and estrogen with regard to feeding behavior is exemplified by results from Santollo and colleagues who showed that ICV MCH increases chow consumption to a greater degree in male rats compared to female rats [135]. Furthermore, female rats that underwent ovariectomy surgeries (OVX) and were treated with estradiol-replacement (mimicking the estrous phase) demonstrated attenuated orexigenic effects of MCH [135, 136]. They also looked at the influence of cyclic endogenous estradiol by measuring chow intake after administration of ICV MCH in estrous and diestrous rats and

found that the orexigenic effect of MCH was specific to increasing meal size without affecting meal frequency, and this meal size enhancement was attenuated in estrous phase rats [135]. These results indicate an effect of estrogen on the MCH system, in which heightened estrogen in female rats attenuates the hyperphagic effects of central MCH.

The neural mechanisms mediating this sex-dependent effect were further investigated recently by our group. Results showed feeding-related interactions between MCH and ERα occur in the ACBsh to promote food intake and motivation for palatable foods in a sex-dependent manner [73]. Either pharmacological activation of MCH1R in the ACBsh or chemogenetic activation of ACBsh-projecting MCH neurons increased the consumption of both chow and sucrose in male, but not female rats [73]. Furthermore, in estradiol-treated OVX rats there was an attenuation of the orexigenic effects of MCH in the ACBsh relative to vehicle-treated rats [73]. Additionally, it was found that female rats had a significantly higher percentage of neurons that express both MCH1R and ERα in the ACBsh compared to males [73]. Overall, these results indicate MCH ACBsh signaling is sex-dependent based on interactions with ERα and identify the ACBsh as a site contributing to this functional interaction.

While ERα and MCH1R overlap in the ACBsh, MCH neurons do not express ERα in the LHA of either male or female rats [137, 138]. However, ERα expressing cells are found in close proximity to MCH neurons in the LHA and IHy [137, 138], suggesting that estrogen may indirectly influence MCH neuron activation. Consistent with this notion, there is a reduction of hypothalamic MCH and MCH1R expression in estradiol-treated OVX rats [138]. Additionally, subcutaneous injection of an ERα agonist is sufficient to reduce MCH and MCH1R protein expression to the same levels as the estradiol treatment [138]. Therefore, ERα may be mediating MCH-induced orexigenic effects in a sex-dependent manner by decreasing the expression of MCH and MCH1R through a yet unidentified indirect pathway.

5. Concluding Framework: MCH drives appetition

A number of findings, including several discussed above, are consistent with a framework in which the food intake-promoting effects of central MCH signaling are based, at least in part, on the enhancement of construct coined by Sclafani and colleagues as “appetition” [139]. Appetition refers to the postoral processes through which intragastric nutrients produce rapid ingestion and flavor preference conditioning, a process that is in contrast to the more classically studied process of satiation whereby nutrients and other GI signals function to reduce intake, leading to meal termination [139]. MCH elevates food intake by selectively increasing meal size without affecting meal number, thus suggesting that both augmented appetition and impaired satiation may contribute to MCH effects on extending a meal. However, Dominigos and colleagues showed that optogenetic activation of MCH neurons during sucralose consumption reverses the preference for sucrose over sucralose while concomitantly elevating dopamine in the striatum [56], suggesting that MCH may act to increase meal size, at least in part, by providing an appetition signal. Given that sucralose shares a similar molecular structure to sucrose and activates sweet taste receptors, yet without stimulating postingestive elevations in blood sugar, it stands to reason that MCH

neurons may drive increases in food intake by producing and/or enhancing postingestive nutritive reinforcement. In further support of the appetition model, given that elevated blood sugar is an early postprandial physiological signal, MCH neurons are depolarized by extracellular, physiologically relevant concentrations of glucose in a dose-dependent manner [49]. Indeed, activation of MCH neurons alone is reinforcing [140], further supporting that the MCH system may be mediating some of the rewarding postoral properties of food consumption.

Perhaps the strongest evidence that the MCH system promotes appetition comes from a recent study revealing that the capacity for MCH neuronal activation (via optogenetics) to acutely stimulate feeding is only observed when optogenetic MCH neuron stimulation occurs after the animals are already eating, suggesting that the intake-promoting effects of MCH occur within the context of the meal vs. influencing preprandial appetitive processes [140]. Also fitting within the framework wherein MCH positively promotes feeding within the context of a meal via increasing the early prandial rewarding properties, there is evidence that both MCH-induced feeding and positive orofacial responses to sucrose requires opioid receptor signaling [129], suggesting that MCH may be enhancing the hedonic gustatory properties of food via interactions with the opioid system.

In light of the aforementioned evidence supporting an MCH-mediated appetition model, Sclafani and colleagues previously investigated whether MCH receptor is necessary for postingestive glucose-mediated flavor-nutrient conditioning. They found, contrary to expectations, that the rewarding post-ingestive properties of glucose remain intact in MCH1R knockout mice [57]. While these data suggest that appetition can occur in the absence of whole-body MCH1R signaling, one important consideration is that there are some limitations with mouse genetic knockout methodology, including putative compensatory actions based on genetic deficiencies during development [141]. Moreover, these results when considered with other results described herein further support a divergence between pharmacological, chemogenetic, and optogenetic manipulations of MCH signaling vs. transgenic ablation of MCH1R. Additional research is required to systematically investigate a role for the MCH system in the early prandial appetition process that enhances consumption within a meal.

In conclusion, it is clear that the MCH system promotes weight gain, with evidence for a stimulatory impact on food intake via action in the ACBsh, PVH, ARH, and cerebrospinal fluid, while promoting food impulsivity without enhancing consumption in the HPCv. A growing amount of evidence supports a model in which MCH’s hyperphagic effects are driven, in part, by promoting the early prandial postoral process of appetition. However, with regard to identifying neural pathways and neurobiological mechanisms through which MCH impacts energy balance and the physiological conditions during which MCH neurons are engaged, there is still much to be discovered. Importantly, while the MCH system has been shown to interact with metabolic parameters (glucose tolerance, insulin and leptin sensitivity), other neuropeptide systems (e.g., orexin, opioids, melanocortins), there is a paucity of data on how each of these parameters are impacted in females, and thus future investigations into this system should include equal representation of the sexes.

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Highlights:

- Melanin-concentrating hormone increases food intake, acting in the arcuate nucleus, paraventricular nucleus, nucleus accumbens shell, cerebrospinal fluid
- Melanin-concentrating hormone interacts with a number of neuropeptides resulting in metabolic consequences
- The orexigenic effect of melanin-concentrating hormone is sex-dependent and likely mediated by estrogen receptor-α
- Melanin-concentrating hormone may be involved in early prandial "appetition" that enhances consumption within a meal