The roles of melanin-concentrating hormone in energy balance and reproductive function: are they connected?

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Abstract

Melanin-concentrating hormone (MCH) is an anabolic neuropeptide with multiple and diverse physiological functions including a key role in energy homeostasis. Rodent studies have shown that the ablation of functional MCH results in a lean phenotype, increased energy expenditure and resistance to diet-induced obesity. These findings have generated interest among pharmaceutical companies vigilant for potential anti-obesity agents. Nutritional status affects reproductive physiology and behaviours, thereby optimising reproductive success and the ability to meet energetic demands. This complex control system entails the integration of direct or indirect peripheral stimuli with central effector systems and involves numerous mediators. A role for MCH in the reproductive axis has emerged, giving rise to the premise that MCH may serve as an integratory mediator between those discrete systems that regulate energy balance and reproductive function. Hence, this review focuses on published evidence concerning i) the role of MCH in energy homeostasis and ii) the regulatory role of MCH in the reproductive axis. The question as to whether the MCH system mediates the integration of energy homeostasis with the neuroendocrine reproductive axis and, if so, by what means has received limited coverage in the literature; evidence to date and current theories are summarised herein.

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Introduction

Energy balance is inextricably linked to reproduction: the ability to monitor both internal and external energy availability and consequently to modulate reproductive behaviours confers a species-wide reproductive advantage (Schneider 2004). In times of energy scarcity, survival of the individual takes precedence over reproductive activities, which bear high energy and nutrient demands. Reproductive disturbances may be evident on either side of the energy balance continuum. It is well established that low energy availability results in adaptive responses that ultimately suppress ovarian function in both humans and female mammals. On the other hand, obesity is also associated with reproductive disorders that may affect both ovarian and neuroendocrine functions (Pasquali *et al.* 2003, Solorzano *et al.* 2012).

These reproductive derangements both in the undernourished and in the obese are unsurprising from an evolutionary viewpoint that propounds survival of the fittest. Hence, those mechanisms that control reproductive function and nutritional status must be functionally linked (Schneider 2004). Nevertheless, in mammals these links are complex and incompletely understood. However, it is evident that there are

myriad hormonal and neuropeptide interactions that ultimately modify gonadotrophin-releasing hormone (GNRH) activity in response to metabolic cues (Evans & Anderson 2012). One neuropeptide that participates in energy homeostasis but has received comparatively little attention within the reproductive context is melanin-concentrating hormone (MCH).

Originally characterised as a circulating hormone modulating the skin colour of teleost fish (Kawauchi *et al.* 1983), mammalian MCH was subsequently identified in rat hypothalamic tissue (Vaughan *et al.* 1989). The majority of anatomical work has been undertaken in the rodent, in which the neuropeptide is expressed primarily, though not exclusively, in the lateral hypothalamic area (LHA) and the rostral zona incerta/incertohypothalamic area (IHy) (Bittencourt *et al.* 1992, Sita *et al.* 2007, Bittencourt 2011): two areas known to be critically involved in the regulation of feeding behaviours. The orexigenic properties of MCH were first proposed in 1996 (Qu *et al.* 1996), although the findings of a number of subsequent studies suggest that the anti-obesogenic effects of MCH antagonism are mediated through its effects on appetite regulation, secondary to its effects on energy expenditure and

altered metabolism (Shimada *et al.* 1998, Chen *et al.* 2002, Marsh *et al.* 2002, Segal-Lieberman *et al.* 2003).

The physiological functions of MCH are not restricted to energy metabolism. Of particular interest to this review are the effects of MCH on the female reproductive axis. To date, the known effects are largely those associated with the central effects of MCH on the regulation of luteinising hormone (LH) release (Gonzalez *et al.* 1997, Murray *et al.* 2000a, 2006, Williamson-Hughes *et al.* 2005). It must be noted that while evidence implicating MCH in the central control of consummatory behaviours and energy expenditure is robust, the role of MCH in the reproductive axis is less well corroborated. For example, although *Pmch*-knockout (k/o) mice are fertile (Shimada *et al.* 1998, Marsh *et al.* 2002, Alon & Friedman 2006, Adams *et al.* 2011), there are no reports in which the efficiency of reproductive function has been fully investigated. Hence, while MCH appears not to be an absolute requirement for normal reproduction, its role(s) as a mediator and/or modulator are as yet ambiguous (see part 3). Evidence to date indicates that the physiological significance of MCH in reproduction may be auxiliary to its better-characterised role: further investigation is required to confirm or deny such an assertion. Hence, this review focuses on published evidence concerning the dual roles of MCH in these discrete yet overlapping systems that modulate energy balance and reproductive function.

Part 1: MCH, appetite regulation and energy expenditure

The pharmaceutical industry is currently very interested in targeting the MCH system as a therapeutic in the treatment of obesity because of its regulatory role in feeding behaviours and energy expenditure, though the development of such a compound has not been without challenges (Mendez-Andino & Wos 2007, Hogberg *et al.* 2012). Of particular relevance are studies that report that the deletion of either the *Pmch* gene or MCH receptor (*Mchr1*) results in resistance to diet-induced obesity (Chen *et al.* 2002, Kokkotou *et al.* 2005, Mashiko *et al.* 2005). Although two MCH receptor subtypes have been

identified in humans, rhesus monkeys, dogs and ferrets (designated MCHR1 and MCHR2), research to date has focused on MCHR1, since functional MCHR2 is not conserved in rodents or rabbits (Tan *et al.* 2002). Due to this evolutionary divergence, the relevance of rodent models to the study of MCH reproductive interactions may be questioned; however, limited research indicates that the most likely physiological roles for MCHR2 are concerned with the modulation of feeding behaviours (Rodriguez *et al.* 2001, Wang *et al.* 2001, Ghousani *et al.* 2007). A summary of key results is presented in Table 1. The behavioural and metabolic effects of MCH on energy homeostasis may be summarised as follows:

Appetitive behaviours

Accumulating evidence from behavioural and anatomical studies supports a role for MCH activity in the hedonic aspects of feeding. Anatomically, central MCH is well placed to integrate energy balance with food reward since the LHA is highly innervated by neuronal input from the nucleus accumbens (NAc), an integral component of the brain's reward circuitry (Grace *et al.* 2007, Mahler *et al.* 2007). It is proposed that the up-regulation of dopamine promotes reward-seeking via neuronal activation of the NAc, which ultimately stimulates feeding by disinhibition of the LHA (for review, see Morton *et al.* (2006)). Food intake, though not energy expenditure, is increased or decreased after injections of MCH agonists or MCHR1 antagonists respectively into the NAc shell (Georgescu *et al.* 2005, Guesdon *et al.* 2009). Anatomically, this area is densely populated by the MCH receptor, as are areas involved in olfaction and gustation (Kokkotou *et al.* 2001, Saito *et al.* 2001). A critical role for MCH in olfaction was proposed by Adams *et al.* (2011), who reported that *Pmch*-k/o mice demonstrated impaired food-seeking behaviours. The infusion of MCH resulted in increased fatty food, alcohol, sucrose and saccharin intake (Gomori *et al.* 2003, Duncan *et al.* 2005, Sakamaki *et al.* 2005, Furudono *et al.* 2006). The antagonism of the MCH receptor via the i.c.v. or i.p. route reduced the consumption of highly palatable or high-fat food (Morens *et al.* 2005, Nair *et al.* 2009), whilst the

Table 1 Summary of results of key mammalian energy balance MCH studies.

Availability of MCH	Experimental intervention	Effect on food intake	Effect on locomotor activity and energy expenditure (EE)/metabolic rate (MR)	Effect on body weight (BW), % fat mass and % lean mass
Increased	Pharmacological/dietary	Hyperphagia/no effect	↓ Locomotor activity	↑ BW; ↑ fat
	Genetic manipulation	Hyperphagia	Not reported	↑ BW; ↑ fat
Decreased	Pharmacological/dietary	Hypophagia/no effect	Not reported	↓ BW; ↓ fat mass
	Genetic manipulation	Hypophagia/no effect/hyperphagia	↑ Locomotor activity; ^a no effect/↑ EE/MR	↓ BW; ↓ fat; no effect/↑ lean mass

Whilst manipulation of the availability of MCH has variable effects on food intake, the effects on locomotor activity/EE/MR and BW/% fat mass/% lean mass are consistent.

^aSome effects were observed in males but not in females.

administration of a MCHR1 antagonist via i.p. injection resulted in reduced sucrose, though not saccharin, self-administration (Karlsson *et al.* 2012). By contrast, hindbrain administration of MCH produced no increase in sucrose, saccharin, food or water intake (Zheng *et al.* 2005, Baird *et al.* 2008). Therefore, it would appear that the orexigenic properties of MCH require forebrain input and that the MCH response to palatable food is related to the nutritive value of the food as well as to the hedonic aspects of feeding.

Consummatory behaviours

In rodents, the MCH system appears to have the capacity to strongly affect feeding behaviours. Hyperphagia or hypophagia can be induced by manipulating the availability of physiological hypothalamic MCH concentrations. While increased availability results in hyperphagia (Ludwig *et al.* 2001, Gomori *et al.* 2003, Santollo & Eckel 2008), decreased availability can result in either hyperphagia (Chen *et al.* 2002, Marsh *et al.* 2002) or hypophagia (Mashiko *et al.* 2005, Kowalski *et al.* 2006). This discrepancy may be attributed to the use of either a genetic or pharmacological rodent model. In pharmacological models, antagonism of MCHR1 resulted in reduced body weight, fat mass and food intake, whereas in genetic models although body weight was decreased or unchanged, food intake in some studies was increased. Compensatory hyperphagia in response to reduced adiposity has been proposed as the cause of increased consummatory behaviours in some *Mchr1*-k/o rodents; this is suggestive of some developmental adaptation in genetic models (for a review, see Pissios (2009)). Therefore, an important distinction appears to be that in pharmacological models altered feeding behaviours are largely responsible for the resultant phenotype, while in genetic models altered energy expenditure accounts for changes in phenotype as feeding behaviours may remain unaltered, increased or decreased (Pissios 2009; Table 1). MCH treatment also seems to be able to affect meal size, which is increased following the administration of MCH (Santollo & Eckel 2008) or decreased following the antagonism of the MCH receptor (Kowalski *et al.* 2006).

Energy expenditure

A putative role for MCH in energy conservation has been validated by findings from genetic studies that have consistently shown that the ablation of functional hypothalamic MCH results in increased energy expenditure and, in some cases, increased locomotor activity (Shimada *et al.* 1998, Marsh *et al.* 2002, Segal-Lieberman *et al.* 2003, Jeon *et al.* 2006). As noted above, this phenomenon does not occur in pharmacological models. Furthermore, in some studies,

elevated energy expenditure was observed in males only (Chen *et al.* 2002, Alon & Friedman 2006). In one study, locomotor activity was decreased following MCH administration (Santollo & Eckel 2008). Interestingly, increased energy expenditure resulting from the decreased availability of physiological hypothalamic MCH may be accompanied by either hyperphagia or hypophagia. Whether these consummatory behaviours are compensation driven (i.e. increased ingestion to compensate for increased energy output) or a result of reduced MCH-induced food intake is not known.

A lack of consistency in terms of the effect of MCH administration/ablation on feeding behaviours contrasts with the reported uniformity of its effects on energy expenditure (Table 1). In those studies where functional MCH or its receptor was ablated, all the animals demonstrated increased energy expenditure (although some sexual dimorphism was observed) resulting from increased metabolic rate, increased locomotor activity or both. The characteristic lean phenotype induced by functional MCH ablation is noteworthy since this property appears to be atypical of other orexigenic mediators such as orexins (Hara *et al.* 2005), neuropeptide Y (NPY) and agouti-related protein (AgRP; for reviews, see Lin *et al.* (2004) and Flier (2006)) and serves to underline the distinctive role of MCH in energy conservation.

Part 2: MCH and reproductive function

While the orexigenic effects of MCH have been well documented, reports concerning the role of MCH in the reproductive axis have been less prolific.

Over the last decade, several groups have investigated the potential role of MCH in the regulation of LH release, either directly at the level of the pituitary or indirectly via the stimulation of hypothalamic GNRH: the focus of this review is the modulatory role of MCH in the hypothalamic regulation of the reproductive axis by GNRH. Anatomically, this is plausible since various studies in female rodents have reported the close apposition of MCH fibres to hypothalamic GNRH neurones (Smith & Grove 2002, Williamson-Hughes *et al.* 2005, Wu *et al.* 2009), and *Mchr1* mRNA has been detected in GNRH neurones (Williamson-Hughes *et al.* 2005). Approximately 85–90% of GNRH neurones were reportedly in contact with MCH-immunopositive projections (Williamson-Hughes *et al.* 2005). This is in agreement with a study, albeit in male mice, that reported that 86% of hypothalamic GNRH neurones were in close apposition with MCH-immunoreactive fibres (Ward *et al.* 2009). Some anatomical overlap was also observed between MCH-immunoreactive projections and GNRH neuroterminals in the median eminence (Ward *et al.* 2009). *In vitro* *Mchr1* mRNA has been detected in GT1-7 cell lines (mouse cell model of hypothalamic GNRH neurones) (Yang *et al.* 2005), although one can speculate

expression in male rats (Mystkowski *et al.* 2000) and hypothalamic PMCH protein expression in female rats (Santollo & Eckel 2013). In ovariectomised primates, an increase in hypothalamic immunoreactive MCH and immunoreactive neuropeptide E-I (NEI) concentrations was detected coincidental with the LH surge 72 h after injection of oestradiol, however, oestradiol concentrations would have been returning to baseline in these animals. MCH-immunoreactive content was not significantly increased 30 h after injection when circulating oestradiol concentrations would be elevated, although the authors do describe them as being 'transiently elevated' (Viale *et al.* 1999).

Pharmacological doses of oestrogen block the increase in hypothalamic PMCH expression customarily induced by caloric restriction (Morton *et al.* 2004). Here, it should be noted that under conditions of prolonged energy insufficiency, circulating oestrogen concentrations would be typically low. While the presence of rapid signalling (non-genomic) oestrogen receptors has not been discounted, there is no evidence of the expression of oestrogen receptors on hypothalamic MCH neurones (Muschamp & Hull 2007, Santollo & Eckel 2013). However, there was considerable anatomical overlap in the distribution of oestrogen receptor-labelled cells and MCH neurones, suggestive of an indirect regulatory mechanism, possibly via an intermediary neurone or ligand that consequently modulates MCH expression (Muschamp & Hull 2007, Santollo & Eckel 2013).

Whilst it would seem that oestrogen treatment is inhibitory to MCH expression in both males and females, MCH appears to be more effective at exerting its biological effect in the presence of oestrogen. The neurones that MCH innervates are therefore hypothesised to be oestrogen-sensitive. MCH may directly innervate GNRH neurones which express ESR2 (ER β) (Herbison & Pape 2001), and/or indirectly via an interneurone that is both MCH and oestrogen sensitive and in turn acts on GNRH. Clearly, the neurocircuitry controlling the hypothalamic–pituitary–gonadal axis is complex and other neuromodulators are known to be involved: leptin, serotonin, dopamine, kisspeptin and NEI have all, for example, been reported to stimulate gonadotrophin release (MacKenzie *et al.* 1984, Vitale *et al.* 1993, Yu *et al.* 1997, Messenger *et al.* 2005, Attademo *et al.* 2006). Precisely where MCH fits into this neurocircuitry is yet to be defined, and the proposed indirect effects of MCH on GNRH via other neuronal populations will be discussed further.

While understanding of the field of kisspeptin physiology is evolving, results of a recent study advocate an inhibitory role for MCH in the reproductive axis via the inhibition of kisspeptin-sensitive GNRH neurones. Electrophysiological recordings demonstrated not only that MCH exerted strong inhibitory effects on a subpopulation of GNRH neurones, but also that the

excitatory effect of kisspeptin on GNRH was completely blocked by MCH (Wu *et al.* 2009). In agreement with earlier work in rodents (Williamson-Hughes *et al.* 2005, Ward *et al.* 2009), MCH-ir fibres were also observed in close apposition with GNRH–GFP neurones in mice (Ward *et al.* 2009, Wu *et al.* 2009). These results are supportive of a modulatory role for MCH at the level of GNRH and add credence to the proposal that the MCH system may act to inhibit reproductive function under conditions of energy insufficiency, when MCH expression is up-regulated. It should be noted that prepubertal animals were used; therefore, in the absence of oestrogen, a stimulatory effect would not be expected.

Neurokinin B (NKB) is a tachykininergic neuropeptide that has recently been implicated as a critical constituent of normal reproductive biology (Topaloglu *et al.* 2009). In various mammalian species, NKB is co-expressed in the arcuate nucleus (ARC) with kisspeptin and dynorphin (DYN) (Goodman *et al.* 2007, Wakabayashi *et al.* 2010), an inhibitory opioid peptide. There is a substantial body of evidence to support the proposal that this trio of ARC peptides known as KNDy are involved in the pulsatile release of GNRH (for a review, see Rance *et al.* 2010). However, much exploratory work is required to understand the regulatory network and mechanisms of action of this circuitry. Of interest to this review is the fact that the neurokinin B receptor (TACR3(NK3)) is highly expressed in a subpopulation of MCH neurones that also express the anorexigenic cocaine- and amphetamine-regulated transcript (CARTPT (CART); Griffond *et al.* 1997, Cvetkovic *et al.* 2004). Tachykininergic innervation of the 'MCH-containing area' (i.e. the LHA and rostromedial IHy) is extensive and complex (Cvetkovic *et al.* 2003). It has been hypothesised that MCH may be involved in reproductive or defensive behaviours since the most medial MCH cell bodies lie within pathways forming circuits regulating the expression of such behaviours (Thompson *et al.* 1996, Cvetkovic *et al.* 2003). On the other hand, only one NKB retrogradely labelled neurone was detected in the ARC following iontophoretic injection into the rostromedial IHy (Cvetkovic *et al.* 2003). Further work is required, but it is tempting to speculate that a subpopulation of MCH neurones that also express CARTPT may participate in a circuitry regulating both reproductive function and energy balance via tachykininergic stimulation.

Part 3: MCH, energy balance and fertility

Nutritional status affects reproductive physiology, and in many mammals reproductive behaviours, thereby optimising both reproductive success and the ability to meet energetic demands. The complex control system entailing the integration of direct or indirect peripheral stimuli with central effector systems involves numerous hormonal and chemical mediators. Neuropeptides, such as MCH, may act in this domain in one of the following ways: i) as

mediators between feeding behaviours and reproductive function (i.e. when variability in metabolic fuel availability induces altered hormonal response and the consequent modulation of feeding behaviours and reproductive function) and ii) as modulators affecting the availability of oxidisable fuels, thereby influencing reproductive behaviours (Schneider 2004). Though MCH is active in both the ingestive and reproductive contexts, investigation into the metabolic pathways through which it may integrate these dual functions has been limited. The tendency to favour male models in energy balance research (e.g. Ludwig *et al.* 2001, Segal-Lieberman *et al.* 2003, Mashiko *et al.* 2005, Bjursell *et al.* 2006) and female models in reproductive studies (e.g. Murray *et al.* 2000b, Garcia *et al.* 2003, Williamson-Hughes *et al.* 2005, Messina *et al.* 2006) may be problematic for intergender extrapolation of results. In metabolic studies, some sexual dimorphism has been reported. For example, increased energy expenditure was observed in both male *Mchr1*-k/o and male transgenic mice with temporal loss of MCH, though not in their female counterparts (Chen *et al.* 2002, Alon & Friedman 2006). To date, the role of MCH in male reproductive physiology has been largely neglected. Since in most species the energy cost of procreation for females far exceeds that for males, a potential gender difference in MCH action would merit investigation.

As discussed earlier, MCH seems to be stimulatory in the reproductive axis only in the presence of oestrogen, while oestrogen appears to be inhibitory to hypothalamic prepro-MCH expression (Murray *et al.* 2000b, Mystkowski *et al.* 2000); the latter phenomenon may be a consequence of negative feedback of oestrogen on MCH. Messina *et al.* (2006) found that oestradiol treatment decreased MCH-induced food intake. Santollo & Eckel (2008) also reported that both exogenous oestradiol and endogenous oestradiol exert a reductive effect on MCH-induced feeding via decreased meal size. Furthermore, a difference in the magnitude of the orexigenic effects of MCH between different stages of the oestrous cycle was observed, with these effects being attenuated in oestrous rats (following high oestradiol secretion) compared with dioestrous rats. Males with lower circulating levels of oestradiol exhibited a greater orexigenic response to MCH infusion than did females. It was thus hypothesised that the characteristic changes in feeding behaviours at different stages of the oestrous cycle in female rats may partly be mediated by altered MCH signalling (Messina *et al.* 2006). Furthermore, both endogenous and exogenous oestrogen reduced PMCH and MCHR1 protein expression in cycling and ovariectomised rats (Santollo & Eckel 2013). In cycling rats, PMCH expression and serum oestrogen were negatively associated and fewer MCH-ir neurones were detected in proestrous rats than in dioestrous and oestrous rats. Hence, the authors propose that cyclical oestrogen-induced suppression of feeding behaviours is mediated via reduced hypothalamic PMCH and MCHR1 protein

content. This appears to be an indirect effect, however, since *in vitro* oestrogen failed to alter PMCH or MCHR1 expression and, in agreement with previous work (Muschamp & Hull 2007), MCH and ESR1 (ER α) were not co-localised, although MCH-ir and ER α -ir neurones were detected in proximity. Hence, it could be argued that MCH acts as a modulator in these scenarios linking female reproductive physiology with ingestive behaviours, since in the presence of oestrogen feeding behaviours are suppressed; therefore, energetic resources may be directed towards reproductive behaviours. Conversely, in the absence of oestrogen (typically under conditions of energy restriction), MCH does not stimulate the reproductive axis and the energetic emphasis may be directed to the restoration of eubalance. Clearly, more work is required under normal physiological conditions.

Significantly, the MCH neuronal population is heterogeneous, and a number of subpopulations have been identified based on their topography, co-expression with other neurotransmitter receptors and peptides, axonal pathways, projections to distinct brain regions or time of genesis (Elias & Bittencourt 1997, Griffond *et al.* 1997, Bittencourt & Elias 1998, Bayer *et al.* 1999, Brischoux *et al.* 2002, Cvetkovic *et al.* 2004, Schéle *et al.* 2012). Hence, it is likely that these discrete populations respond to different stimuli and may act through different pathways. There has been a tendency to overlook these distinctions in research to date, which could be a source of equivocality with regard to the roles of MCH; for example, if a specific subpopulation of MCH neurones interface with an oestrogen-sensitive mechanism, this may partly explain the phenomenon that MCH seems to exert its effects only in the presence of oestrogen.

Pregnancy and lactation present considerable physiological challenges to the organism. Lactation, in particular, is characterised by substantially increased energy demands and a marked increase in food intake in rats (Ofedal 2004). *Pmch* expression was transiently induced in the hypothalamic POA and rostral parts of the paraventricular nucleus of dams 8–21 days *postpartum* (Knollema *et al.* 1992). Others have since reported similar results (Sun *et al.* 2004, Rondini *et al.* 2010); however, one research group has reported the converse; that is, a decrease in hypothalamic *Pmch* mRNA expression in pregnant and lactating rats (Garcia *et al.* 2003). Mice in which a time-dependent ablation of MCH neurones was orchestrated were not capable of rearing their offspring (Alon & Friedman 2006). *Pmch*-k/o mice had smaller, lighter litters with poorer survival rates than wild-type mice (Adams *et al.* 2011); these studies indicate a role for MCH in lactation and maternal behaviour. Though *Pmch*-k/o mice are fertile (Shimada *et al.* 1998, Alon & Friedman 2006, Adams *et al.* 2011), the dubious health of the offspring in the latter study suggests compromised uterine growth and/or *postpartum*

development. Anterograde tracer injections in lactating rats revealed dense projections from medial POA neurones to areas involved in the control of gonadotrophin expression and female sexual behaviours (Rondini *et al.* 2010). Specifically, there was a significant increase in MCH innervation of the ventrolateral subdivision of the ventromedial nucleus of the hypothalamus and the ventral premammillary nucleus, leading the authors to propose that MCH may be acting to inhibit reproductive function and behaviours during lactation via this pathway. A further finding that the MCH neurones of the mPOA co-express the inhibitory GABA-synthesising enzyme glutamic acid decarboxylase provoked the hypothesis that the MCH/GABA neurones may inhibit pulsatile LH secretion during lactation (Rondini *et al.* 2010) via the close apposition of MCH and NEI terminals to GNRH cell bodies (Smith & Grove 2002, Williamson-Hughes *et al.* 2005, Ward *et al.* 2009, Wu *et al.* 2009) or via MCHR1, which is co-expressed in a subpopulation of GNRH neurones (Williamson-Hughes *et al.* 2005). Finally, since the mPOA MCH neurones of female rats were in close apposition to terminals immunoreactive for AgRP, α -melanocyte-stimulating hormone and CART, neurobiological regulators clearly implicated in energy balance (Rondini *et al.* 2010), it could be that the mPOA is one site where MCH is active in the integration of ingestive and reproductive behaviours, at least in conditions of negative energy balance that are customary during lactation.

Summary

The portfolio of the multiple and diverse physiological functions of MCH, both metabolic and behavioural, continues to expand. Over the last two decades, its role as a crucial mediator of energy balance has become apparent. The known activities of MCH in the reproductive axis are chiefly those associated with the regulation of LH release and the effect of oestrogen on MCH expression. MCH may stimulate or inhibit LH release depending on oestrogenic milieu, and MCH expression may be oestrogen-dependent. Furthermore, in female rats, cyclic modulation of feeding behaviours may be partially mediated by altered MCH signalling. The complexities of the inter-relationship between ingestive and reproductive behaviours are slowly being unravelled, and MCH is undoubtedly a component of this neurocircuitry, though the extent and scope of its molecular interactions are still being documented. Evidence to date suggests that, in the reproductive context, MCH is a modulator rather than a primary regulator. However, as the MCH story unfolds, questions are both answered and posed, and manipulation of the availability of MCH and its receptor in different animal models has provided some important insights into its physiological relevance.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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