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# Melanocortinergic control of penile erection

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## Abstract

Melanocortin receptors in the forebrain and spinal cord can be activated by endogenous or synthetic ligands to induce penile erection in rats and human subjects. To better understand how melanocortin circuits play a role in sex behavior, we review the contribution of melanocortin receptors and/or neurons in the hypothalamus, hindbrain, spinal cord and peripheral nerves to erectile function. New information regarding neuropeptides that mediate penile erection has extended our understanding of the central control of sex behavior, and melanocortin agonists may provide alternatives to existing treatment for highly prevalent problems including erectile dysfunction.

### Keywords

MSH; Proopiomelanocortin; Hindbrain; Sex behavior

## 1. Introduction

Penile erection requires the activation of parasympathetic vasodilator pathways and inhibition of sympathetic penile vasoconstrictor tone to create full penile rigidity. One well-described excitatory circuit originates in the parvocellular region of the paraventricular nucleus of the hypothalamus, uses oxytocin (OT) as the neurotransmitter and projects to extrahypothalamic sites including the sacral spinal cord [2,7,12,16,24]. A second putative excitatory pathway with both hypothalamic and spinal loci is mediated by melanocortin (MC) receptors [57]. While the inter-relationship of OT and MC systems in the control of penile erection has not been completely determined, a growing body of evidence suggests that melanocortinergic output pathways play an important role in the control of sex behavior. Furthermore, the MC receptor agonist MT-II induces penile erection in humans and a close analog, PT-141, shows promise as a therapeutic agent for erectile dysfunction [13,45]. A summary of the structure and function of α-MSH and these synthetic peptides and their affinity for MCR 1, 3–5 is shown in Table 1.

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Recent advances in the understanding of MC mediated erection have been driven by novel synthetic MC receptor ligands as well as MC receptor deficient animal models [5,6,20,21]. The explosion of interest in the central control of energy balance and satiety has yielded insights into potential circuits controlling food intake that may be relevant to reproduction and sex behavior [10,47,48]. The purpose of this article is to summarize the current research findings implicating melanocortins in penile erection and to identify deficiencies in the field. We have organized this review according to the supraspinal, spinal, and peripheral distribution of melanocortin receptors and the specific aspects of erectile control that this localization is likely to subserve. Greater understanding of the neural circuitry, melanocortin receptor specificity, and interaction with other proerectile pathways may enhance our understanding of the pathophysiology of erectile dysfunction as well as clinical applications of melanocortin agonists in the treatment of sexual dysfunction.

## 2. Forebrain MC neurons and receptors and penile erection

### 2.1. Hypothalamic nuclei

The effects of α-MSH and ACTH on sexual excitement in rodents has been recognized since 1968 [9]. Secretion of α-MSH in sexual situations has been demonstrated in the MPOA in male rats and in response to gonadal steroids in female rats [25,38,39]. Whether α-MSH has a facilitatory or inhibitory effect on sex behavior may be gender specific [44]. MC agonists activate sexual appetite in addition to penile erection and the stretching yawning syndrome, suggesting a forebrain effect [3,42,56]. Central administration of α-MSH and ACTH in male rats produces penile erection due to an action in the regions surrounding the third ventricle [2]. The specific nuclei in which α-MSH acts include the PVN, dorsomedial nucleus, ventromedial nucleus, and anterior hypothalamic area [3]. Melanocortins also has satiety effects in areas within the dorsal vagal complex based on responses to both fourth ventricle and lateral ventricle injections [59].

It is not known whether the release of α-MSH is necessary for penile erection or other sex behaviors. Hypothalamic regions innervated by projections from POMC-expressing Arc neurons include the lateral hypothalamus, dorsal medial nucleus, and the PVN. In one study systemic administration of PT-141 to rats led to penile erection and increased c-fos expression in the PVN [41]. Because pro-opiomelanocortin (POMC) neurons have a restricted distribution in the CNS, functional neuroanatomical studies may be able to elucidate the proerectile role of MC signals generated in the arcuate nucleus (Arc) of the hypothalamus and the caudal portion of the NTS of the hindbrain [26,27].

### 2.2. Receptor specificity

Only MCR3 and MCR4 are expressed in the central nervous system [58]; the relative contribution of each to melanocortin-induced erection has not been finalized. Nonspecific MC agonists such as MT-II induce erections when administered into the lateral ventricle of rats [57] or subcutaneously to human subjects [55]. Van der Ploeg et al. [51] used pharmacological and genetic tools to demonstrate that MCR4 receptors play a role in sexual function. $MCR4^{-/-}$ mice had impaired reflexogenic and copulatory behavior compared to wild type controls and showed diminished erectile responses to the MCR4 agonist THIQ.

Unlike the nonspecific MC receptor agonists, which have been shown to initiate erections in humans without sexual stimulation, no evidence exists in animals that THIQ can initiate spontaneous erectile events. This raises the possibility that both MCR3 and MCR4 are required for the full proerectile actions of MT-II and PT-141. Additional evidence using selective MC receptor antagonists is conflicting. In one study the MCR4 antagonist HS014 only partially abolished α-MSH induced erection in rats, leading Vergoni et al. [53] to attribute penile erectile actions to MCR3. Using the same antagonist Argiolas et al. [3] reported no reduction in α-MSH or ACTH induced erections. Given that the relative affinity of HS014 for MCR4 is only 10-fold greater than MCR3, this compound may not be sufficiently selective to pharmacologically identify the MC receptor(s) responsible for induction of erection in the brain. Alternatively, the dose of HS014 in both studies may not have been sufficient to rule out a possible MCR4 driven mechanism. Studies using Cre/lox inducible genetic targeting [46] or more selective agonists and antagonists with full dose response curves will be necessary to further define the role of the two receptor subtypes in the forebrain control of penile erection.

## 3. Hindbrain MC neurons and penile erection

Neurons in the hindbrain have been implicated in the control of penile erection via their relationship to hypothalamic as well as spinal pathways [4,15]. Elimination of hindbrain catecholaminergic projections to the medial hypothalamus, which have been reported to be glucoresponsive, significantly attenuated penile reflexes in rats and altered the expression of hypothalamic neuropeptides that stimulate penile erection [15]. In another study, paraventricular neurons were found to send direct projections onto neurons that innervate the penis via descending serotonergic raphe-spinal neurons. The rostral nucleus paragigantocellularis is one group of brainstem nuclei implicated in this inhibitory pathway [4,31,33,34].

Whereas no role has been demonstrated for hindbrain MC receptors or neurons in penile erection, the localization of POMC neurons in the NTS and their contribution to other homeostatic regulatory pathways provide indirect evidence that hindbrain MC signaling may contribute to the supraspinal control of penile erection. This would not be surprising given the low likelihood that multiple systems subserving different aspects of sex behavior would all be mediated at same site. MC control of energy metabolism in the forebrain and hindbrain provides an example of this phenomenon. An independent caudal brainstem MCR3/4 trigger for sympathetically stimulated metabolic responses has been reported [59]. Furthermore, MC receptor agonist effects on energy homeostasis can be mediated by circuitry intrinsic to the caudal brainstem and spinal cord. Existing data also suggests that release of oxytocin from a descending parvocellular PVN-to-NTS pathway contributes to leptin's attenuation of food intake by a mechanism that involves the activation of PVN oxytocin neurons by leptin [11,28,29]. It is intriguing to consider that a similar oxytocinergic pathway may exist to activate NTS POMC neurons projecting to sympathetic or parasympathetic nuclei controlling erectile function in the distal spinal cord.

## 4. Spinal MC receptors in penile erection

Coordination of ascending and descending input controlling penile erection is thought to be carried out by spinal mechanisms [36]. In addition to the known presence of OT projections and OT receptors on sacral parasympathetic nuclei innervating the corpus cavernosum [16,17,54], a proerectile function of MC receptors in the spinal cord has been proposed based on pharmacological, molecular, and immunohistochemical findings. POMC neurons from the Arc and retrochiasmal area innervate sympathetic preganglionic neurons in the thoracic spinal cord [14], and in the lumbar region of the spinal cord POMC and MCR4 mRNA has been demonstrated [50,51]. Localization of MC receptors is consistent with pharmacological studies from our laboratory demonstrating a spinal site of action for the melanocortins [57]. In the rat intrathecal injection of MT-II at the level of the lumbar enlargement induced penile erections in a dose-dependent fashion, an effect that could be blocked with the nonspecific MC receptor antagonist SHU-9119. Yawning, a behavior closely associated with neuropeptides administered to the forebrain, was not observed with intrathecal MT-II administration. That these erections were not the result of activation of MC receptors in the forebrain was further supported by the finding that i.c.v. SHU-9119 did not block the erections and that the time course for erections after i.th. and i.c.v. injection was similar [57]. What particular subset of neurons expresses MC receptors, and what function these neurons have, remain unknown. One mechanism by which spinal MC signaling modulates erectile function has been suggested by recent studies in spinalized rats [1]. In this model MT-II is thought to facilitate proerectile responses through effects on thoracolumbar sympathetic neurons but not via sensory afferent or sacral parasympathetic nerves. Thus, MC circuits may contribute to penile erection by lifting the inhibitory constrictor tone on the cavernosal smooth muscle.

## 5. Peripheral receptors

MC agonists do not directly modulate smooth muscle relaxation or constriction in the corpus cavernosum. Intracavernosal MT-II neither increased intracavernous pressure nor augmented neurostimulated erectile responses in one study [57].Nor did the same peptide cause cavernosal smooth muscle relaxation in vitro, confirming findings with THIQ on isolated cellular responses [51,52]. However, the localization of MCR4 in stretch activated mechanoreceptors and sensory afferent nerves of the human penis raises new questions as to peripheral contribution of MC ligands and other peptides on erectile function. MC receptors could potentially modulate sensory afferent signals from the penis and genitalia during sexual activity, thus enhancing descending proerectile signaling. Whether the constitutive signaling activity of these MC receptors, or others controlling penile erection in the CNS, is activated by circulating MC peptides or conversely suppressed by one of the endogenous inverse agonists such as Agouti or Agouti Related Peptide has not been investigated [23].

## 6. Oxytocin-MC interactions

Redundancy in signaling systems is an established finding within peripheral erectile tissues. Whether oxytocin and melanocortin signaling during penile erection is redundant or subserve different proerectile pathways remains to be determined. Hypothalamic oxytocin

projections to sacral parasympathetic nuclei suggest a direct proerectile function. Neither such circuits have been demonstrated for MC's, nor has the interaction between the two pathways been completely outlined. Antagonists of dopamine or oxytocin receptors do not block the proerectile action of supraspinal α-MSH [8,40]. Martin et al. [35] recently showed that the MCR4 agonist THIQ enhanced ex-copula erections, and that this effect could be blocked by systemic or central administration of an oxytocin antagonist. The divergence in findings may relate to the multiple loci of dopamine, oxytocin, and melanocortin receptor action within the CNS, the relative affinity of the ligands, or limitation of the models (Fig. 1). It is possible that spinal but not forebrain erectile signaling from MC receptors requires activation of OT receptors. Additionally, signals from MCR3 and MCR4 may converge on oxytocinergic neurons at different sites in proerectile pathways.

## 7. Clinical implications

### 7.1. Pathophysiology

In one experimental model of diabetic erectile dysfunction, autonomic neuropathy accounted for only a part of the dysfunctional findings, and spinal sexual reflexes were severely impaired [37]. Although abnormal hypothalamic signaling has not been implicated as a pathophysiological mechanism of either male or female sexual dysfunction, streptozotocin diabetic rats become unresponsive to the erectile effect of ACTH as early as eight days after induction of hyperglycemia [43]. Experimental diabetes also has profound effects on leptin sensitive POMC neuronal signaling in the hypothalamus: rats and mice exhibit reductions in lateral Arc POMC mRNA expression in response to fasting and streptozotocin induced diabetes [22,49]. Fraley has shown that immunolesion of hindbrain catecholaminergic projections to the medial hypothalamus attenuates penile reflexive erections via an action on glucoresponsive neurons [15]. Further studies are necessary to determine whether selective dysfunction in POMC neuron populations or MC receptor expression could in part mediate the sexual dysfunction apparent in diabetes.

### 7.2. Therapeutic applications

Novel pharmacological therapies remain a priority because of the high prevalence of sexual dysfunction in men and women and the failure of phosphodiesterase-based therapy for some patients with erectile dysfunction [19,30,32]. New agents targeting the central nervous system, and especially the spinal cord, are of considerable interest [18]. The potential favorable safety profile, rapidity of onset, and possible effects on sexual motivation all make central initiators attractive alternatives to phosphodiesterase inhibitor therapy for erectile dysfunction. Administration of PT-141, a nonselective MC receptor agonist (see Table 1), initiated penile erections without video sexual stimulation (VSS) in normal volunteers, and in a Phase IIA study significantly augmented erectile activity in response to VSS in men with erectile dysfunction who had previously responded to sildenafil citrate [13,45]. Significant differences in real time penile tumescence responses were noted between placebo and doses greater than 7 mg intranasal. The proerectile effect was dose-dependent with limited side effects (flushing and nausea) and no syncope or hypotension. In the Phase II study of men with ED, the compound appears to be extremely potent, inducing sustained erectile activity that subsides with cessation of video sexual stimulation. The cessation of

erectile responses with termination of VSS confirms, in addition to known initiator action, the facilitatory action and sexual usefulness of PT-141. PT-141 appears to be a promising candidate for further evaluation in at-home trials (Phase IIB) as a treatment for male ED.

## 8. Conclusions

The presence of melanocortinergic neurons or receptors at all central and peripheral nervous system loci of erectile signaling, and the powerful proerectile effects of melanocortin agonists strongly suggest involvement of melanocortin signaling in the complex circuits controlling penile erection. Critical portions of this proposed circuitry remain unexamined, including the relative contribution of MCR3 and MCR4 at different CNS sites, interaction of MC signals with the oxytocinergic pathways emerging from the PVN, the role of hindbrain POMC neurons in supraspinal and spinal signaling, and the identity of distal spinal cord neurons expressing MCR4. The recognized therapeutic benefits of this class of proerectile drug strongly points towards the clinical relevance of melanocortins in sex behavior. However, important conceptual questions regarding the role of melanocortinergic signaling in normal erectile function, and its potential perturbation by disease states associated with ED, require validation and study in animals.

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## Abbreviations

| | |
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| **ARC** | arcuate nucleus |
| **D** | dopamine receptor |
| **MC** | melanocortin |
| **MCR** | melanocortin receptor |
| **MSH** | melanocyte-stimulating hormone |
| **NTS** | nucleus of the solitary tract |
| **OT** | oxytocin |
| **POMC** | proopiomelanocortin |
| **PVN** | paraventricular nucleus |

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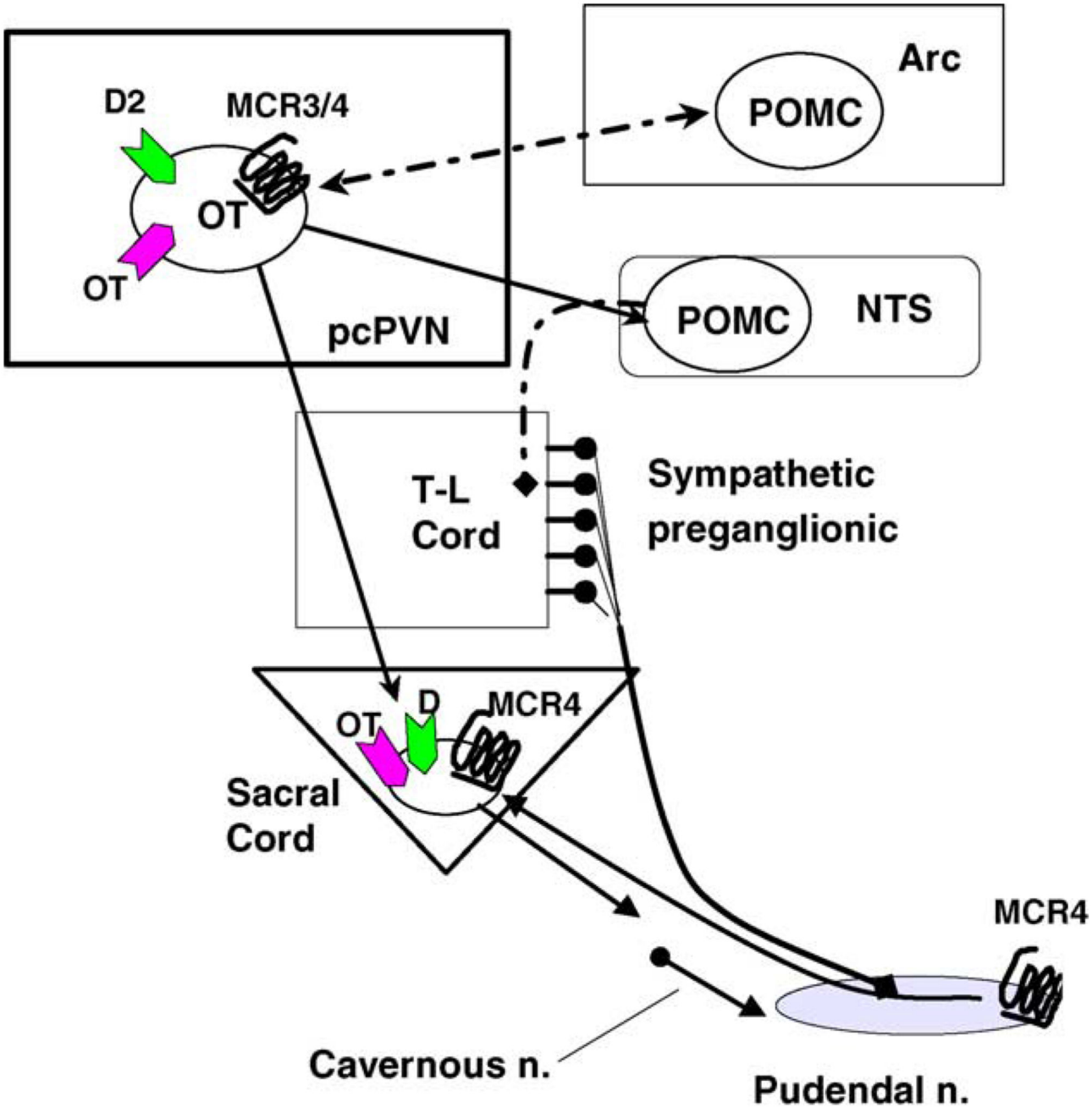


**Fig. 1.**

Proposed MC output pathways involved in the initiation and facilitation of penile erection. In this model, POMC neurons in the arcuate nucleus (Arc) release α-MSH in the parvocellular PVN (and other hypothalamic nuclei not shown) in response to sensory or other input due to sexual stimuli. Parvocellular OT neurons project to extrahypothalamic sites including the sacral spinal cord as well as the NTS. The proerectile signal originating from OT receptors in the sacral cord may be augmented by additional MC signaling, either from forebrain projections on excitatory neurons or via a hindbrain effect to suppress

thoracolumbar sympathetic constrictor tone in the corpus cavernosum. Additional contribution from sensory afferent nerves containing MC4 receptors may also play a role.

**Table 1**

Structure and affinity of α-MSH, MT-II, and PT-141

| Peptide | Structure | MCR1 | MCR3 | MCR4 | MCR5 |
|---|---|---|---|---|---|
| α-MSH | Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-$NH_2$ | 0.12 | 31 | 660 | 5700 |
| MT-II | Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-$NH_2$ | 0.67 | 34 | 6.6 | 46 |
| PT-141 | Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-OH | ? | ? | 15 | ? |

$K_i$ values (in nM) of natural and synthetic peptides for MC receptors 1, 3, 4, and 5 reported in the literature using essentially the same binding conditions [from references [41,58], and personal communication, D. Earle, Palatin Technologies, November 2, 2004].