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Review

# Discovery that a melanocortin regulates sexual functions in male and female humans

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**Abstract**

Melanocortins (MCs) are multifunctional peptide hormones that regulate a diversity of physiological functions. MCs have been implicated in sexual function in animals. We document here that a MC analog, Melanotan II (MTII), can enhance sexual function in human males (erectile activity) and females (increased levels of sexual desire and genital arousal). Unlike other sexual-enhancement drugs, MTII works at the level of the brain, thus eliciting a rather natural sexual response with minimal or no undesirable side effects. The actions of the peptide were discovered accidentally while studying the effects of the peptide and related analogs on human skin pigmentation (tanning).


*Keywords:* Melanocortins; MTI and MTII; MSH

Melanocyte stimulating hormone (MSH); the name defines its major role as was established early in the twentieth century (about 1910–1920) [5]. The function of MSH was clearly established in animals such as frogs and lizards and other cold-blooded animals, but only recently was the hormone also shown to control skin coloration/pigmentation in humans [6]. In fact, we now realize that MSH and related melanocortins (MCs) regulate a diversity of functions as mediated through a multitude of MC receptors (MCRs). Most interesting was the relatively recent discovery that a MC regulates sexual function in humans [8,11–13].

There was for several decades a knowledge that a MC probably regulated some aspect of sexual function in animals [3,10], but not humans. There never was any evidence that MSH or ACTH (corticotropin) played a role in reproductive physiology when administered systemically in animals. But when delivered directly into the third ventricle of the brain of animals, sexual behaviors were elicited suggesting that a MC might act within the central nervous system (CNS) to control sexual function [3]. A role for a MC in human reproductive function provides an interesting story which emphasizes the old adage that "Chance favors the prepared mind," or put another way, "Keep your eyes open in the laboratory for the unexpected." In the present context, discovery was such an uplifting event that it could not have gone very easily without notice.

Around 1984, in collaboration with Victor Hruby (University of Arizona Chemistry Department) and his students (e.g., Tomi K. Sawyer), we synthesized and biologically characterized some superpotent melanotropic peptides [9]. One of these [Nle$^4$, DPhe$^7$]-substituted MCs, referred to as Melanotan I (MTI), was licensed for commercialization as a tanning agent (Fig. 1). This MC is well on its way toward development for use as a potential "therapeutic tan," a "tan from inside-out," with minimal need for prolonged sun exposure [4].

During the development of MTI, I served as a proverbial "human pincushion" (a.k.a., guinea pig), that is, I tested the efficacy of the peptide to produce a tan on myself. Therein lies a very interesting story. Our group of University investigators (Hadley, Hruby and his student Fahad Al-Obeidi) prepared and characterized some fragment [Nle$^4$, DPhe$^7$]-substituted MC analogs that proved to be as potent as MTI, even though structurally only half the size (seven amino acids) of the parent analog [1,2]. In addition, the melan-

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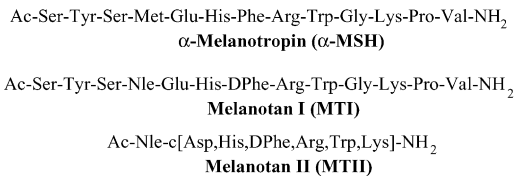


Fig. 1. Comparative primary sequences of α-MSH and two superpotent analogs, MTI and MTII.

otropin, MTII, Ac-Nle-c[Asp, HisDPhe, Arg, Trp, Lys]-$NH_2$, was conformationally restrained by a lactam bridge to provide a cyclic structure of increased lipophilicity (Fig. 1). The smaller molecule is just as active as the larger MTI; it is cheaper to synthesize and might gain access more readily into the body. Based upon these and other considerations, a sterile preparation was provided for injection to determine its tanning potential.

One mistake in my deliberations was made, however. MTI had previously been administered at a dose as high as 10 mg without physiological consequences (other than tanning). I forgot, however, that MTII was only about half the molecular weight of MTI (Fig. 1). Therefore, when I took an equivalent (10 mg) dose of MTII, I inadvertently received about twice the number of molecules of the peptide. Unlike MTI, however, MTII caused a rather immediate, unexpected response: nausea and, to my great surprise, an erection (no figure provided). While I lay in bed with an emesis pan close by, I had an unrelenting erection (about 8 h duration) which could not be subdued even with a cold pack. When my wife came upon the scene, she proclaimed that I "must be crazy." In response, I raised my arm feebly into the air and answered, "I think we may become rich."

Realizing the importance of the observation, I was determined to find out what a lower dose of MTII might do. So several days later, I used half (5 mg) of the previous dose. This again elicited an immediate erection which, however, only lasted about 5 h with somewhat less nausea. Again, at a later date, I cut the dose in half (2.5 mg), and this resulted in an erection of only 2–3 h duration, with only minimal nausea. I now knew I was on the right track. So when I administered about half the previous dose (1.25 mg) there was no nausea and only a feeble wobble, a response which, however, could be rather easily coaxed to a full erectile response following a few erotic reflections. Further experimentation demonstrated that a dose of about 1.5–2.0 mg of MTII invariably induced a full erection without much conscious effort in myself and other volunteers. MTII was licensed to Palatin Technologies (Elizabeth, NJ; Palatin@aol.com). To my knowledge, MTII (referred to by Palatin as PT-141, and by myself as erectide) has never failed to induce an erection in men with claimed impotence but known to be able to achieve an erection as proven by monitoring nocturnal penile tumescence (by a meter, a "peter meter"?). MTII, like other peptides, cannot as yet successfully be delivered by the alimentary (oral) route. MTII, however, is presently being effectively delivered as a nasal spray ("sniff a stiff").

As noted in another manuscript in this journal collection (Hadley and Dorr), MTII may prove equally effective in women wherein it might be useful in the treatment of female sexual dysfunction (FSD). In both men and women, MTII apparently works at the level of the CNS. This conclusion rests upon the earlier observations of Italian investigators who showed that injections of MCs into the third ventricle of the brains of rats caused stretching and yawning ("SYS syndrome") in addition to increased sexual behaviors [3]. When I first discovered the dramatic erectile response to an overdose of MTII, I also noted (as I lay in bed) that I was constantly vigorously stretching and yawning (acting like a rat). We can conclude, therefore, that MTII, unlike MTI, is able to cross the blood–brain barrier to mediate its actions in the brain as a neurohormone.

Unlike Viagra® which can cause a dangerous lowering of blood pressure, MTII appears to have no undesirable side effects at the therapeutic dose used. Patient verbal responses appear to indicate a clear preference for MTII over Viagra®. This may relate to actions of the drug on the brain to cause an enjoyable arousal response which slightly precedes the subsequent erectile response. This observation is similar to that for hypothalamic neurohormones (e.g., follitropin and lutropin) which are known to elicit behavioral responses (e.g., courtship activity) that act in conjunction with peripheral actions on the gonads (e.g., steroid production) to ensure successful sexual function.

The rather immediate action of MTII allows the participant to be sure that he/she is ready for an amorous encounter. No guess work; you do not have to first engage in a sexual endeavor and "hope for the best." This may be why up to about 50% of the men taking Viagra® are unsatisfied with the drug and are seeking an alternate therapeutic remedy. Viagra® also is not effective in every individual. MTII appears to be failsafe–it appears to be 100% effective. Undoubtedly, there must be some men with so severe a problem that they will not be able to benefit from MTII use.

The above story, although initially based upon less scientific methodology than is usually undertaken in the conventional university research laboratory, has been further documented by hundreds of other individuals. The importance of the initial discovery (an erectile response) was immediately recognized for its significance as was also the earlier discovery of the unique action of MTI. As reported elsewhere [7], injections of MTI into a golden retriever resulted in the growth of black hair in a previously all-yellow dog. The potential use of MTI as a possible tanning agent was obvious. Both these observations with MTI and MTII prove the old adage that, indeed, "Chance favors the prepared mind."

## References

[1] Al-Obeidi F, Castrucci AM, Hadley ME, Hruby VJ. Potent and prolonged acting cyclic lactam analogues of α-melanotropin: design based on molecular dynamics. J Med Chem 1989;32:2555–61.

[2] Al-Obeidi F, Hadley ME, Pettitt BM, Hruby VJ. Design of a new class of superpotent cyclic α-melanotropins based on quenched dynamic stimulations. J Am Chem Soc 1989;111:3413–6.
[3] Argiolis A, Meles MR, Gessa GL. Yawning and penile erection: central dopamine–oxytocin–adrenocorticotropin connection. Ann N Y Acad Sci 1988;525:330–7.
[4] Dorr RT, Ertl G, Levine N, Brooks C, Bangert JL, Broome Powell M, et al. Effects of a superpotent melanotropic peptide in combination with solar UV radiation on tanning of the skin in human volunteers. Arch Dermatol 2004;140:827–35.
[5] Hadley ME. The melanotropic hormones. In: Brake D, editor. Endocrinology. 4th ed. New York, NY: Simon & Schuster; 1982. p. 153–76.
[6] Krude H, Biebermann H, Grüters A. Mutations in the human proopiomelanocortin gene. Ann N Y Acad Sci 2003:233–9.
[7] Johnson PD, Dawson BV, Dorr RT, Hadley ME, Levine N, Hruby VJ. Coat color darkening in a canine in response to a potent melanotropic peptide. Am J Vet Res 1994;55:1593–6.
[8] Molinoff PB, Shadiack AM, Earle D, Diamond LE, Quon CY. PT-141: a melanocortin agonist for the treatment of sexual dysfunction. Ann N Y Acad Sci 2003;994:96–102.
[9] Sawyer TK, Sanfillippo PJ, Hruby VJ, Engel MH, Heward CB, Burnett JB, et al. [Nle4, DPhe7]α-melanocyte-stimulating hormone: a highly potent α-melanotropin with ultra long biological activity. Proc Natl Acad Sci USA 1980;77:4754–8.
[10] Thody AJ, Wilson CA, Everard D. Facilitation and inhibition of sexual receptivity in the female rat by α-MSH. Physiol Behav 1979;22:147–50.
[11] Wessells H, Fuciarelli K, Hansen J, Hadley ME, Hruby V, Dorr RT, et al. Synthetic melanotropic peptide initiates erections in men with psychogenic erectile dysfunction: double-blind crossover placebo-controlled study. J Urol 1998;160:389–93.
[12] Wessells H, Levine N, Hadley ME, Dorr RT, Hruby VJ. Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. Int J Impotence Res 2000;12(4):574–9.
[13] Wessells H, Gralnek D, Dorr RT, Hruby VJ, Hadley ME, Levine N. Effect of an alpha-melanocyte stimulating hormone analog on penile erection and sexual desire in men with organic erectile dysfunction. Urology 2000;56:641–6.