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Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II

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We review our experience with Melanotan II, a non-selective melanocortin receptor agonist, in human subjects with erectile dysfunction (ED). Melanotan II was administered to 20 men with psychogenic and organic ED using a double-blind placebo-controlled crossover design. Penile rigidity was monitored for 6 h using RigiScan. Level of sexual desire and side effects were reported with a questionnaire.

In the absence of sexual stimulation, Melanotan II led to penile erection in 17 of 20 men. Subjects experienced a mean of 41 min Rigiscan tip rigidity > 80%. Increased sexual desire was reported after 13/19 (68%) doses of Melanotan II *vs* 4/21 (19%) of placebo ($P < 0.01$). Nausea and yawning were frequently reported side effects due to Melanotan II; at a dose of 0.025 mg/kg, 12.9% of subjects had severe nausea.

We conclude that Melanotan II is a potent initiator of penile erection in men with erectile dysfunction. Our findings warrant further investigation of melanocortin agonists and antagonists on penile erection. *International Journal of Impotence Research* (2000) **12,** Suppl 4, S74–S79.

Keywords: penile erection; MSH; sex behavior; impotence

Introduction

Alpha-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropin (ACTH), known as the melanocortins, have been implicated in the control of penile erection and sex behavior in animals.[1–5] Five melanocortin receptor (MC-R) subtypes have been cloned, and reveal different functions based on localization.[6] MC1-R and MC2-R are the classical melanocytic and adrenocortical receptors in the skin and adrenal cortex respectively.[7,8] MC3-R is principally present in the brain, with low levels of expression in the gut.[9] MC4-R is restricted to the nervous system; blockade of this receptor partially abolishes αMSH-induced erection in rats.[5] MC5-R has been localized in exocrine and endocrine glands including the reproductive tract of the rat.[6,7]

Melanocortins influence important homeostatic behaviors mediated by the hypothalamus. Melanocortinergic neurons exert a tonic inhibition of feeding behavior. Chronic disruption of this inhibitory signal by the agouti peptide is a likely explanation of the agouti obesity syndrome in mice.[10] The agouti peptide is an MCR-4 antagonist. Melanocortins regulate sexual behavior including penile erection, sexual motivation, and, in the female rat the secretion of sexual attractants from the preputial gland.[6] α-MSH and ACTH are believed to act downstream from dopamine and oxytocin in the hypothalamic proerectile centers adjacent to the third ventricle.[2] MC5-R expression among peripheral tissues provides a functional coherence between central and peripheral control of sex behavior.[6]

A number of melanocortin agonists have been synthesized to enhance skin pigmentation.[11] Melanotan I, a linear peptide analog of α-MSH, causes tanning.[12] Melanotan II, a cyclic non-selective melanocortin receptor agonist, initiates erections in rats, dogs, and humans.[13,14] We report our experience with Melanotan II in human subjects with erectile dysfunction (ED).[13,15]

Materials and methods

Subjects

Men aged 18–75 y with a chief complaint of ED were enrolled in two studies.[13,15] In Study 1 men with no organic etiologies and normal nocturnal penile tumescence (> 10 min of tip rigidity > 70%)

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were enrolled and designated as having psychogenic erectile dysfunction. Men with ED and major organic risk factors were enrolled in Study 2. The pertinent characteristics of the study populations are listed in Table 1. Erectile dysfunction was defined as the persistent inability to obtain and maintain an erection sufficient for sexual satisfaction.[16] The Human Subjects Committee of the University of Arizona approved the studies, and written informed consent was obtained on all subjects.

Peptide chemistry:

Melanotan II is a synthetic cyclic heptapeptide, Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-NH_2, which contains the 4–10 melanocortin receptor binding region common to ACTH and MSH, but with a lactam bridge and four amino acid substitutions (Figure 1).

Table 1 Comparison of patient data in two studies (mean values)

Variable	*Study 1 (psychogenic)*	*Study 2 (organic)*
n	10	10
Age (y)	47.4	56.2
Testosterone (mg/ml)	450	362
Pre study NPT events	2.9	2.7
NPT tip rigidity > 70%(min)	47.4	9.3
Organic risk factors	0	2.2

Drug synthesis and purification were carried out as previously described.[17]

Experimental design

A double blind, placebo-controlled crossover design was used. Melanotan II (0.025–0.157 mg/kg) and vehicle were each administered by the investigator twice by subcutaneous injection for a total of four injections; study drug doses were separated by at least 48 h. The order of administration was randomly assigned.

Penile erection was measured with real-time RigiScan monitoring in the home situation (Figure 2). Subjects were instructed to avoid erotic stimuli and to remain awake for the 6-h session. Subjects recorded the number and duration of erectile events. In Study 2, sexual desire was scored from 1 to 5 using a modification of IIEF question 12.[18] Side effects (none, mild, moderate, or severe) were recorded for: nausea; yawning or stretching; facial flushing; decreased appetite; increased appetite; and drowsiness. Subjects denoted onset of symptoms, duration, and measures taken to relieve them. Antiemetics were not prescribed.

Statistical analysis

Mean values of RigiScan parameters after Melanotan II and placebo were compared with the one-tailed

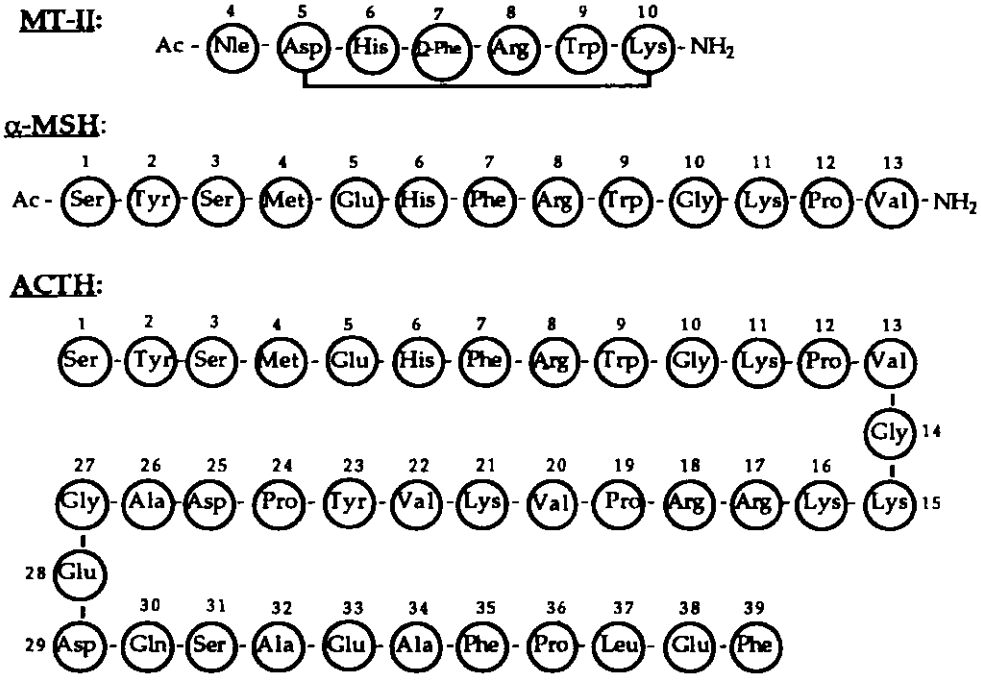

Figure 1 Structure of Melanotan II, α-MSH, and ACTH. Reprinted with permission.[14]

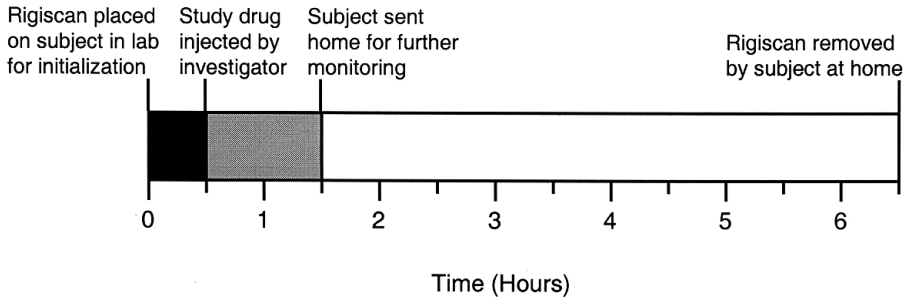

Figure 2 Schema of the experimental protocol. Reprinted with permission.[13]

Student's *t*-test. Side effects due to Melanotan II and placebo were compared with Fisher's exact test.

Results

Twenty subjects aged 22–67 y (mean 51.6 y) were enrolled and completed the studies between July 1995 and December 1998.[13,15] Thirty-nine total injections of Melanotan II were given and 41 of placebo (one subject received three placebo injections and one of Melanotan II due to erroneous administration of vials discovered after completion of the study). No patient withdrew because of side effects.

Of 20 subjects, 17 reported subjectively apparent erection on at least one of two injections of Melanotan II. Overall, erectile activity was reported with 27/39 (69%) Melanotan II injections and 1/41

Table 2 Real-time RigiScan activity after Melanotan II (MT II) and placebo (mean values)

	Psychogenic study		*Organic study*	
RigiScan parameter	*MT II Study 1*	*Placebo Study 1*	*MT II Study 2*[a]	*Placebo Study 2*
% of injections with response	75	0	63	4.7
Erectile events (no.)	3.45	2.35	2.66	0.7
Erectile latency (min)	127.5	NA	97.8	NA
Total erectile duration (min)	163.4	54.5	97.5	25.3
Tip rigidity 80–100%(min)	38.0	3.0	45.3	1.9
Tip rigidity 60–79%(min)	40.3	4.5	10.1	1.1
Tip rigidity activity units	78.4	9.8	58.6	4.54
Tip tumescence activity units	49.7	13.6	29.1	6.0

[a]RigiScan data based on 16 injections due to loss of data from three injections in three subjects, one of whom who reported no erection and two of whom had significant erections (60 and 90 min duration, 9/10 rigidity by visual analog scale).[15]

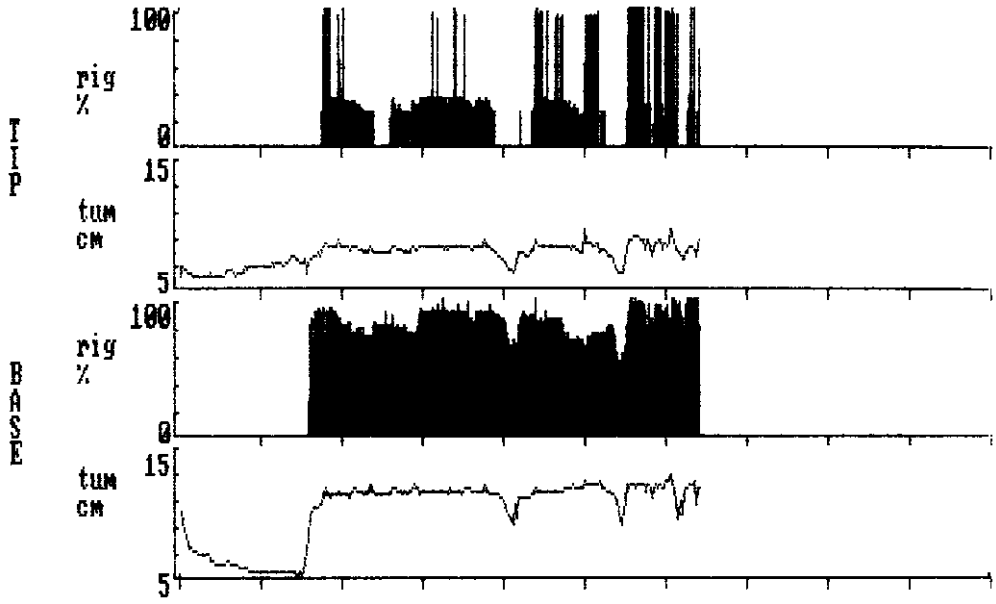

Figure 3 RigiScan tracing of a subject with organic ED who experienced penile erections after 0.025 mg/kg Melanotan II. Note the intervals without significant tip rigidity.

placebo injections ($P < 0.01$). Twelve subjects responded to each Melanotan II injection, five responded to only one of two doses, and three men had no erectile activity with Melanotan II.

RigiScan results showed statistically significant differences in erectile activity between Melanotan II and placebo (Table 2). Latency to first erection ranged from 15 to 270 min (mean 115). Duration of rigidity between 80 and 100% ranged from 0 to 254 min on Melanotan II (mean 41.0). Tip Rigidity Activity Units were 78.4 and 58.6 in psychogenic and organic ED patients respectively ($P = 0.49$). The subject with 254 min of rigidity had two episodes of complete detumescence dividing the erections (see Figure 3), and no subject reported a painful erection.

Heightened sexual desire was reported in Study 2 after 13/19 (68%) doses of Melanotan II *vs* 4/21 (19%) of placebo ($P = 0.0034$). Table 3 shows the individual responses. Of the 10 subjects reporting a moderate or high level of desire, all but one developed a penile erection. Mean level of sexual desire (scale 1–5) was 2.47 after Melanotan II *vs* 1.24 on placebo ($P < 0.001$).

Nausea and stretching/yawning occurred significantly more frequently with Melanotan II than placebo (Table 4), but no serious or unexpected adverse events occurred. Nausea was reported with 15/39 (38%) injections of Melanotan II, including severe nausea in six cases (15.3%, $P < 0.05$ *vs* placebo). One subject vomited in association with an episode of severe nausea. Four of 31 (12.9%) injections of 0.025 mg/kg Melanotan II led to severe nausea. No subject experienced severe nausea with both administrations of Melanotan II, and symptoms were reduced, in eight of 11 instances, on second dosage of the drug.

Table 3 Effect of Melanotan II on sexual desire[a]

Sexual desire[b]	*MT II* $n = 19$	*Placebo* $n = 21$
Very low or none at all	6	17
Low	3	3
Moderate	5	1
High	5	0
Very high	0	0

[a]Data from Study 2 only.[15]
[b]Modified Question 12 of IIEF.[18]

Table 4 Clinically important side effects of Melanotan II and placebo

Side effect	*Melanotan II* *(n = 39)*	*Placebo* *(n = 41)*
Nausea		
None	23	37
Mild	8	3
Moderate	1	0
Severe	6[a]	1
Stretch/yawn		
None	17	36
Mild	14	3
Moderate	5	2
Severe	3	0

[a]Two of these six subjects received > 0.1 mg/kg Melanotan II.

Discussion

Melanotan II, a non-specific MCR agonist, initiates erections in men with organic and psychogenic erectile dysfunction. Seventeen of 20 subjects reported penile erection, although not with each administration. The majority of erections induced by Melanotan would be considered sufficient for sexual intercourse: tip rigidity time > 80% averaged 41 min. The magnitude and duration of erectile activity was greater in the psychogenic ED patients than organic ED patients, although this difference was not statistically significant. The nature and severity of the erectile dysfunction was not completely characterized in these studies, making comparison of results between the two groups difficult. We found no significant correlation between duration of prestudy NPT and response to Melanotan II, although subjects only underwent one night of NPT testing.

The mean erectile latency time of 112.6 min for Melanotan II is long for a clinically useful drug. However, the addition of erotic stimulation may lead to responses that are more rapid. It is possible that the RigiScan device, through intermittent constriction of the penis, provides some sexual stimulation. Melanotan II in all likelihood must cross the blood brain barrier for its activity, which may explain the prolonged time to peak effect. Modification of drug delivery may enhance acceptability for clinical use. The time at which nausea was first reported, on average 168 min after injection, suggests that the gastrointestinal side effects are centrally mediated as well. The exact locus of action of Melanotan II remains unknown, but strong circumstantial evidence points to a central mechanism. Intracerebroventricular administration of Melanotan II in rats leads to erection and yawning, and no change in intracavernous pressure was observed after intracavernous injection (unpublished data). Melanotan I, a non-cyclic MCR agonist that does not cross the blood brain barrier, has no erectogenic activity. Further animal studies using selective melanocortin antagonists and agonists and receptor localization will be necessary to identify its pharmacological mechanism.

We could not differentiate Melanotan II responders from non-responders based on NPT criteria, testosterone levels, or etiology of ED. Our combined data make it unlikely that Melanotan II could be used as a diagnostic tool to differentiate organic and psychogenic etiologies. Differences were noted in the onset and duration of erectile activity between

psychogenic and organic subjects. In the absence of pharmacokinetic data on these subjects, any explanation of these differences remains speculative. It is intriguing to consider, however, that psychogenic inhibition of arousal may contribute to a delayed onset of erectile activity, whereas organic etiologies reduce the total duration and magnitude of response.

The increased sexual desire scores after Melanotan II may reflect the wording of IIEF question 12, which describes sexual desire as 'wanting to have a sexual experience, thinking about having sex, or feeling frustrated due to lack of sex'.[18] These responses certainly would not be surprising in men with ED who develop penile erections and cannot engage in sexual activity. Investigation of this finding in subsequent home use studies would be essential before further commercialization of the drug.

The safety profile of Melanotan II is acceptable: no serious adverse event occurred, and only one subject requested antiemetic therapy. Nausea and stretching/yawning were reported more commonly after Melanotan II than placebo in both studies. While 38% of subjects reported nausea, the incidence of severe nausea at our preferred dose of 0.025 mg/kg was 12.9%. We noted a reduction in the incidence and severity of nausea with the second administration of the drug, suggesting a first dose effect. Only one subject reported skin pigmentation, and a cumulative dose of 0.1 mg/kg is necessary for skin tanning.[14]

Yawning occurred with a significantly higher frequency after Melanotan II than placebo. We believe that this phenomenon is analogous to the stretching/yawning syndrome observed in rats. The stretching/yawning syndrome, an ancestral vestige that subserves arousal, is mediated by hypothalamic centers in proximity to the paraventricular nucleus.[2]

Melanotan II may eventually prove to be beneficial for patients with ED. However, the incidence of severe nausea and prolonged latency time raise questions about the potential clinical applications of the drug.[15] The pharmacokinetics and lowest effective dose of Melanotan II must be determined in order to reduce side effects without reduction in erectogenic activity.

Conclusions

Melanotan II, a non-selective MCR agonist, initiated penile erections in 69% of administrations in men with psychogenic and organic ED. Mean duration of real-time RigiScan tip rigidity > 80% was 41 min; the time to onset (mean 112 min) was longer for men with psychogenic ED compared to those with organic ED, although the former group had more sustained rigidity and a higher overall response rate. Side effects of nausea and yawning/stretching occurred more frequently with Melanotan II than with placebo, including a 15.3% incidence of severe nausea. The observation of increased sexual desire with Melanotan II is novel and warrants further investigation. Further studies to localize the site of action and receptor subtype mediating the action of Melanotan II may allow development of targeted receptor-specific melanocortin therapy for ED.

Acknowledgement

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Appendix

Open discussion following Dr Wessells' presentation

Dr Broderick: Did you do any stimulation studies to see if you could increase the onset of erection and increase the duration of erection?

Dr Wessells: We are currently conducting a study with a few men where we're collecting pharmacokinetic data. We're showing them videos and sexual stimulation, so, hopefully I'll have an answer for you on that.

Dr Broderick: Were your men doing any daytime napping at home?

Dr Wessells: They were instructed not to sleep, and a flaw of the study was that we should have kept the men in the clinic rather than sending them home.

Dr Broderick: Do you believe these men were desirous of sexual activity?

Dr Wessells: There were some men who felt an increase in desire. They were stimulated, but it's going to take more studies to sort that out. We're always looking at drugs and saying we don't want them to increase sexual desire, but there may come a time where we try and develop a class of drugs that will increase desire.

Dr Nehra: The RigiScan itself is somewhat stimulating and may promote more erectile activity.

Dr Wessells: All of them were also evaluated with placebo, but yes, there may have been some sexual stimulation from the RigiScan.