ABSTRACT

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Facilitator proerectile activity of Melanotan II (MT-II) in anesthetized rats

Julien Allard[1], Laurent Alexandre[1], Jacques Bernabé[1], Gérard Benoit[2], Stéphane Droupy[2], François Giuliano[1,2*]

[1] PELVIPHARM Laboratories, Gif-sur-Yvette, France [2] Medical University of Paris South- Research Group in Urology. Le Kremlin-Bicêtre, France * e-mail address: giuliano@cyber-sante.org

ABSTRACT

Introduction and Objective: MT-II, a cyclic peptid analog of alpha-MSH, exhibits agonist activity at 4 of the 5 known melanocortin receptors i.e. MC1R, MC3R, MC4R, MC5R. The ability of MT-II to induce penile erections without any sexual stimulation has been demonstrated in conscious and anesthetized rats. Because a selective MC4R agonist was shown to facilitate penile erection in anesthetized rat (PNAS, 2002, 99:11381), we assessed whether MT-II could display proerectile facilitator activity and sought for the site of action for such an effect.

Methods: Intracavernous (ICP) and blood pressure (BP) were monitored in urethane-anesthetized Sprague Dawley rats. Erectile responses were elicited by electrical stimulation of the cavernous nerve (1 ms, 6 V, 3 Hz or 5 Hz for 45 s) before and after intravenous injection of 1 mg/kg MT-II or vehicle (saline). The ratio of the rise in ICP over corresponding BP (ΔICPmax/BP) was computed for each frequency before and after MT-II or saline injection. ΔICPmax/BP after MT-II or saline injection was then expressed as the % of ΔICPmax/BP before MT-II or saline injection for each frequency (%ΔICPmax/BP). To locate the site of action of MT-II, proerectile facilitator activity was assessed in rats submitted to bilateral transections of I) the pelvic nerves (PNx), or ii) the dorsal nerve of the penis (DNPx), or iii) removal of the lumbar paravertebral sympathetic chain (LSCx).

Results: %ΔICPmax/BP (mean±standard error of the mean) obtained in each group is given with result of the comparison between vehicle and MT-II injection with t-test. In brackets is the number of rats in each group. CT: control rats.

	3 Hz				5 Hz			
	CT (10)	PNx (8)	DNPx (9)	LSCx (10)	CT	PNx	DNPx	LSCx
Veh (%)	87±9	141±11	105±7	112±7	89±5	127±13	94±2	110±7
MT-II (%)	128±17	195±18	145±12	119±12	127±12	188±17	127±10	131±8
p	0.04	0.03	0.01	0.64	<0.01	0.01	<0.01	0.07

MT-II displayed a significant proerectile facilitator activity in control, PNx and DNPx rats. The proerectile facilitator effect was not anymore significant in LSCx rats.

Conclusions: MT-II displays significant facilitator proerectile activity in urethane-anesthetized rats. Persistence of the proerectile activity of MT-II in DNPx and PNx rats rules out an action on sensory afferences from the penis and on proerectile input issued from the spinal parasympathetic nucleus respectively. The decrease of the facilitator proerectile activity of MT-II after removal of the LSC points to an involvement of the sympathetic pathway to the penis in this effect.

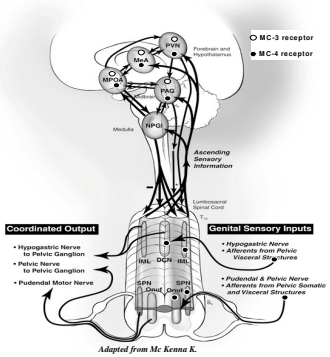
BACKGROUND

➢Melanotan II (MT-II) is a cyclic synthetic peptide analog of α-MSH with an agonist activity at 4 of the 5 known melanocortin receptors: MC1R, MC3R, MC4R, MC5R.

➢Melanotan II is a potent initiator of erections in men with psychogenic and organic erectile dysfunctions (Wessels et al., 2000).

➢MT-II induces penile erection in conscious and anesthetized rats (Wessells et al., 2003a;2003b).

Potential sites of action for MT-II

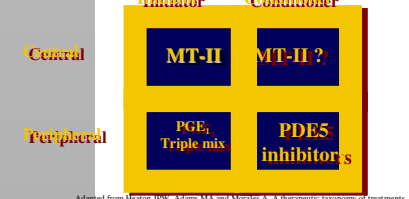


Adapted from Mc Kenna K.

OBJECTIVES

➢To assess whether MT-II displays proerectile facilitator activity in anesthetized rats.

➢To determine the site(s) of action for the facilitator/conditioner effect of MT-II.



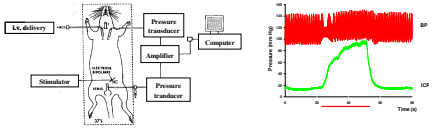
Adapted from Heaton JPW, Adams MA and Morales A. A therapeutic taxonomy of treatments of erectile dysfunction: an evolutionary imperative. *Int J Impotence Res. 1997;9:115-121.*

METHODS

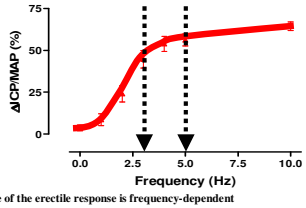
Evaluation of the facilitator effect of MT-II on erectile function

➢ Urethane-anesthetized male Sprague-Dawley rats (225-250 g).

➢ Evaluation of erectile response by simultaneous monitoring of the arterial blood pressure (BP) and intracavernous pressure (ICP) following electrical stimulation of the cavernous nerve (45 s duration, 6 V, 1 ms pulse) performed twice in a randomized order every 90 s.



Results are expressed as the increase in intracavernosal pressure (ICP) following electrical stimulation, normalized by the mean arterial pressure (BP) of the animal.



➢ Amplitude of the erectile response is frequency-dependent

⇒ The facilitator effect of a treatment on an erectile response elicited by cavernous nerve stimulation can be evidenced using electrical parameters eliciting submaximal or maximal erectile responses :

-Electrical stimulations were performed before and after intravenous (i.v.) injection of vehicle (saline) or MT-II (1 mg/kg) at 3 and 5 Hz.

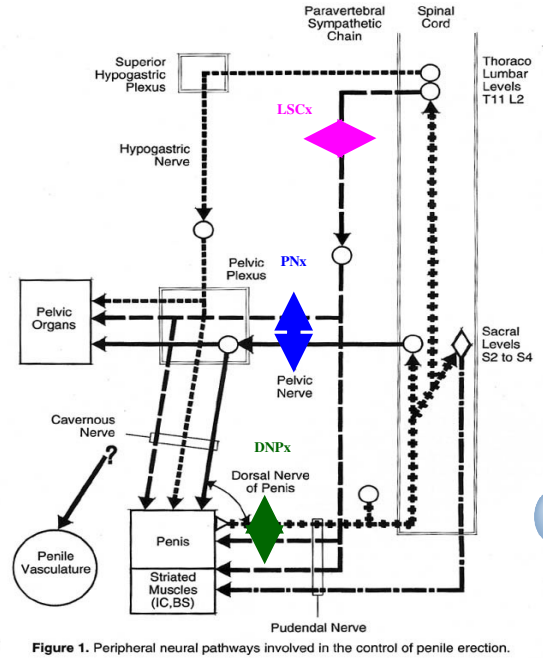


Figure 1. Peripheral neural pathways involved in the control of penile erection.

➢ Control rats (CT) or bilateral transections of :

- ❖ Pelvic nerves (PNx).
- ❖ Dorsal nerve of the penis (DNPx).

removal of:

- ❖ Lumbar paravertebral sympathetic chain (LSCx).

Transections or removal:

References

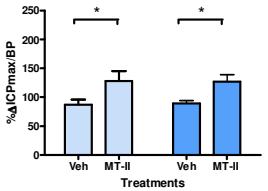
➢Wessells H, Gralnek D, Dorr R, Hruby VJ, Hadley ME, Levine N (2000). Effect of an alpha-melanocyte stimulating hormone analog on penile erection and sexual desire in men with organic erectile dysfunction. Urology. 56(4):641-646.

➢Wessells H, Hruby VJ, Hackett J, Han G, Balse-Srinivasan P, Vanderah TW (2003a). MT-II induces penile erection via brain and spinal mechanisms. Ann N Y Acad Sci. 994:90-95.

➢Wessells H, Hruby VJ, Hackett J, Han G, Balse-Srinivasan P, Vanderah TW (2003b). Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-NH2 induces penile erection via brain and spinal mel anocortin receptors. Neuroscience. 118(3):755-762.

RESULTS

Control rats (CT)

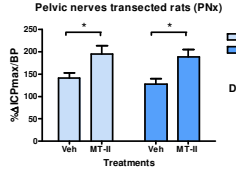


(n=10 in each treatment group)

➢ MT-II displayed a significant proerectile facilitator acti

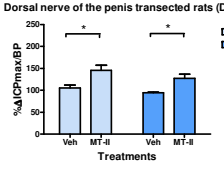
**p<0.05, Student's t-test*

Pelvic nerves transected rats (PNx)



(n=8 in each treatment group)

Dorsal nerve of the penis transected rats (DNPx)

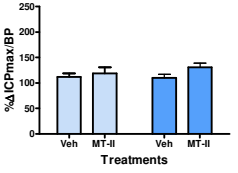


(n=9 in each treatment group)

➢ The proerectile facilitator activity remained after PNx and DNPx.

**p<0.05, Student's t-test*

Lumbar paravertebral sympathetic chain removal (LSCx)



(n=10 in each treatment group)

➢ The proerectile facilitator activity was abolished after LSCx

**p<0.05, Student's t-test*

SUMMARY OF RESULTS

➢MT-II (1 mg/kg) induced a significant proerectile facilitator activity in urethane-anesthetized control rats (CT).

➢Bilateral transection of the pelvic nerves (PNx), which convey the proerectile parasympathetic fibers issued from the sacral sympathetic nucleus to the penis, did not abolish the proerectile facilitator effect of MT-II (1 mg/kg).

➢Bilateral transection of the dorsal nerves of the penis (DNPx), did not abolish the proerectile facilitator effect of MT-II (1 mg/kg).

➢In contrast, bilateral removal of the lumbar paravertebral sympathetic chain (LSCx) at the L4-L5 level together with the inferior mesenteric ganglion significantly decreased the proerectile facilitator activity of MT-II (1 mg/kg).

CONCLUSION

➢The involvement of sensory afferences from the penis in the proerectile facilitator effect of MT-II (1 mg/kg) was ruled out by the lack of effect of dorsal penile nerve transection.

➢Transection of the pelvic nerves did not significantly affect the proerectile activity of MT-II (1 mg/kg), making the involvement of this major proerectile pathway in the facilitator/conditioner activity of MT-II unlikely.

➢The dramatic reduction of the facilitator proerectile activity of MT-II (1 mg/kg) in rats after removal of the lumbosacral paravertebral sympathetic chain points to a potential activity of MT-II on the sympathetic efferences to the pelvis.

➢This finding desserves further investigation in order to answer the following question: does MT-II alter the sympathetic tone to the penis and/or penile vasculature?