MP54-13

A POTENTIAL NEW TARGET FOR STRESS URINARY INCONTINENCE: A μ-OPIOID RECEPTOR IN THE SPINAL CORD ACTIVATED BY A SELECTIVE AGONIST [D-Ala^2, NMe-Phe^4, Gly-ol^5]-enkephalin IN RATS

[1]Department of Urology, [2]Department of Systems Physiology,
Graduate School of Medicine, University of the Ryukyus
Asuka Ashikari[1], Keiichiro Izumi[1], Ryu Kimura[1], Takuma Oshiro[1], Seiichi Saito[1], Minoru Miyazato[2]

Introduction

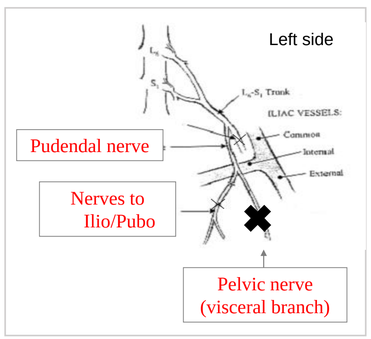
- Stress urinary incontinence (SUI) is the most common type of urinary incontinence in women. Urethral hypermobility (UH) and intrinsic sphincter deficiency (ISD) are two main causative factors of SUI.
- ISD has been reported to be more prominent, however, due to the lack of an effective ISD treatment, UH mid-urethral sling surgery to correct UH is the gold standard treatment.
- We have previously reported that tramadol, which acts as a μ-opioid receptor agonist while it also inhibits norepinephrine and serotonin reuptake, enhanced the urethral continence reflex by activating the peripheral sympathetic pathway and μ-opioid receptors in the spinal cord in rats (Ashikari, Neurourol Urodyn 2018).
- Nevertheless, the precise role of μ-opioid receptors from the spinal cord and their implication in the urethral continence reflex using a selective μ-opioid receptor agonist have not been examined yet.

Aims

We investigated the intravenous or intrathecal effect of a selective μ-opioid receptor agonist, [D-Ala^2, NMe-Phe^4, Gly-ol^5]-enkephalin **(DAMGO)** on the urethral continence reflex in rats.

Animals and Operation

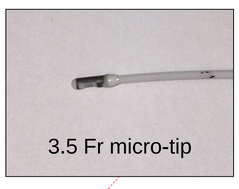
- Female Sprague Dawley rats (weight :180-300 g)
- The bilateral pelvic nerves were transected to block the bladder contraction.

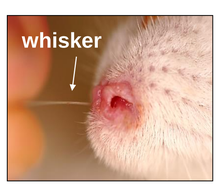


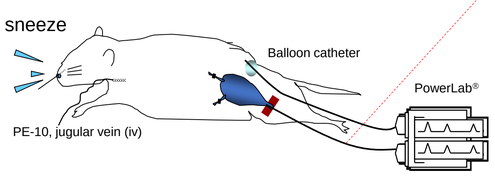
Manzo et al., *Physiol Behav*, 2000

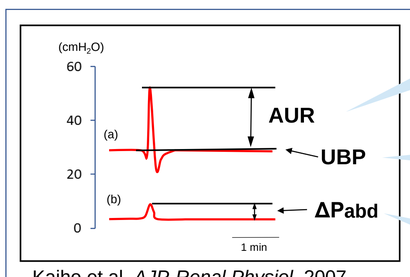
Evaluation of SUI

① Microtip-catheter methods (Experiment1,2)









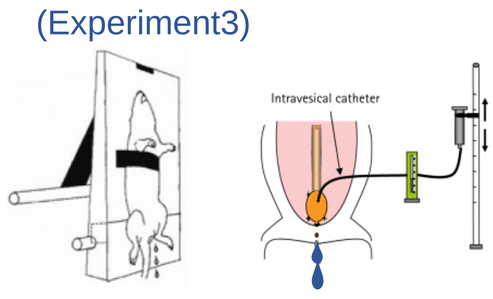
External urethral sphincter activity
(amplitude of urethral response during sneezing)

Urethral smooth muscle activity
(urethral baseline pressure)

Intensity of sneeze
(abdominal pressure)

Kaiho et al. *AJP-Renal Physiol.* 2007

② tilt-Leak Point Pressure (LPP) method (Experiment3)



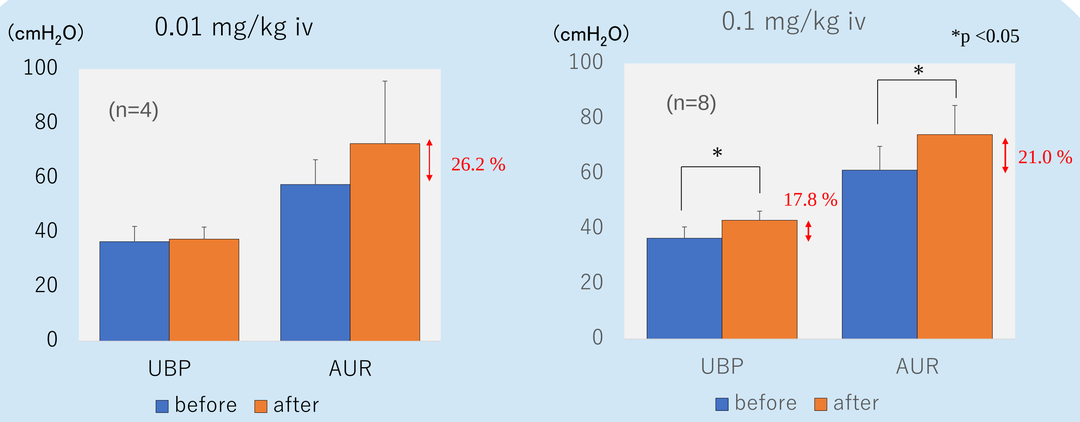
Conway DA et al. *Int. Urogynecol. J. Pelvic Floor Dysfunct.* 2005

LPP : the lowest pressure at which blue-color saline leaked from the urethral meatus

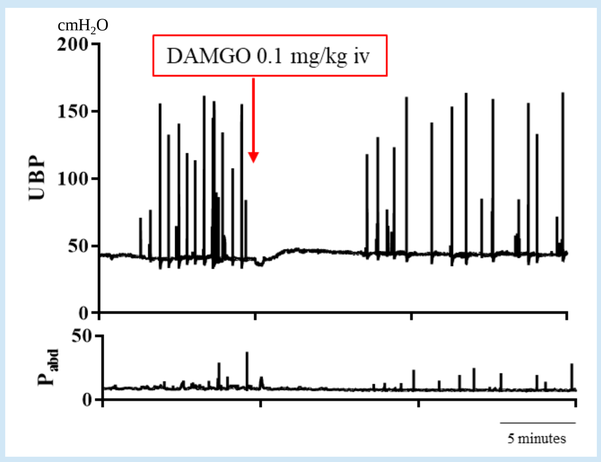
- Experiments were conducted under urethane anesthesia.

Methods and Result Experiment 1

- To investigate the effect of DAMGO on mid-urethral responses during sneezing, urethral baseline pressure (BP) and amplitude of urethral responses during sneezing (AUR) were measured using a microtip transducer catheter.
- The catheter was inserted in the middle urethra before and after an intravenous (iv) injection of DAMGO (0.01 and 0.1 mg/kg).



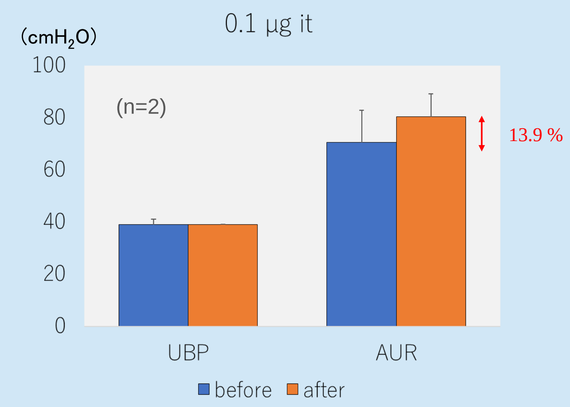
- DAMGO (0.01 mg/kg iv) did not enhance BP and AUR significantly.
- DAMGO (0.1 mg/kg iv) increased BP (36.6±4.1 and 43.1±3.3 cmH$_2$O before and after iv, respectively, P < 0.05) and AUR (61.3±8.6 and 74.2±10.6 cmH$_2$O before and after iv, respectively, P < 0.05).

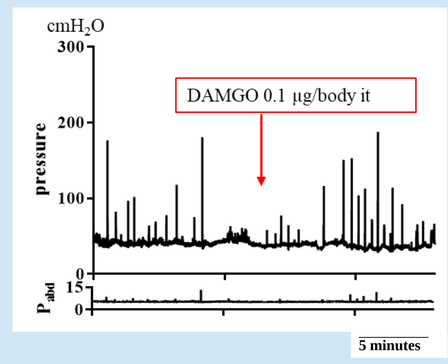


P$_{abd}$:abdominal pressure

Methods and Result Experiment 2

- BP and AUR were measured before and after the intrathecal injection (it) of DAMGO (0.1 μg/body).

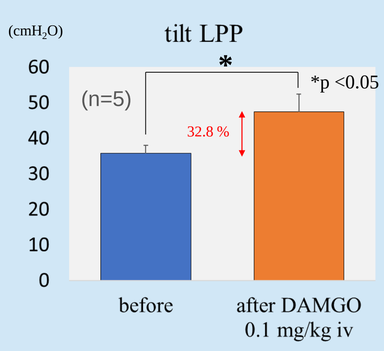


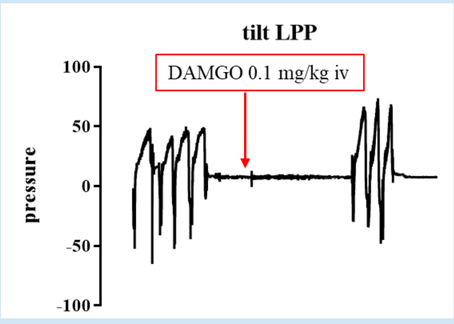


- DAMGO (0.1 μg/body it) increased the AUR by 13.9%, but not the BP.

Methods and Result Experiment 3

- Tilt LPP measurements were conducted to study the effects of DAMGO on the whole urethra.





- DAMGO (0.1 mg/kg iv) significantly increased the tilt LPP (35.7±2.3 and 47.4±4.9 cmH$_2$O before and after iv, respectively, P < 0.05).

Conclusion

- These results indicate that DAMGO, a selective μ-opioid agonist, can effectively enhance the active urethral continence reflex during sneezing at the spinal level (a microtip transducer catheter measurement).
- DAMGO-induced enhances of urethral continence reflex may be due to two pathways.
  1. EUS innervated by pudendal nerves through spinal μ-opioid receptors.
  2. Urethral smooth muscle through central and peripheral sympathetic pathway.
- Therefore, selective μ-opioid receptors activation in the spinal cord may represent a new SUI treatment target in human patients.