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THE INHIBITORY EFFECTS OF GHRELIN ON THE MICTURITION REFLEX IN URETHANE-ANESTHETIZED RATS

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INTRODUCTION

- Ghrelin, a 28 amino acid growth hormone, is widely distributed throughout the peripheral and central nervous systems (1).
- Ghrelin's many physiological functions include growth promotion, suppression of inflammation, and enhancement of food intake (2).
- Increasingly, evidence suggests an antinociceptive role of ghrelin in murine pain models (3).
- However, whether ghrelin also plays a role in controlling the micturition reflex is unclear.

OBJECTIVES

To investigate the effects of intravenous administration of ghrelin on the micturition reflex in rats.

METHODS

Adult female Spraque-Dawley rats (weighing 228-252 g) were used. Rats were maintained under standard laboratory conditions with a 12-h light/12-h dark cycle and free access to food pellets and tap water.

Drugs

Ghrelin (Tocris Bioscience, Ellisville, MO) was dissolved in saline.

Intravenous administration of ghrelin

- Rats were anesthetized with isoflurane followed by urethane (1.2 g/kg subcutaneously).
- A midline abdominal incision was made, and a transvesical catheter (PE-50) with a fire-flared tip was inserted into the dome of the bladder and secured with silk thread for bladder filling and pressure recording. A 3-way stopcock was connected to the transvesical catheter to monitor the bladder pressure.
- Saline was continuously infused into the bladder for 2 hours at a rate of 0.04 ml per minute to record cystometrograms during a control period.
- Stable micturition cycles were established, and ghrelin (300, 600, and 900 µg/kg, n=6 per dose) was then administered intravenously and changes in bladder activity were monitored.
- In another group of animals, ghrelin (900 µg/kg, n=6) was administered intravenously when the first bladder contraction was observed after intravenous administration of naloxone, an opioid receptor antagonist (3 mg/kg, n=6) to determine whether the effect of ghrelin was mediated by the opioid systems.
- Intravenous injections were made through a cannula (PE-10) inserted into the right jugular vein.
- Cystometric parameters were recorded and compared before and after drug administration.

Statistics

- All data values are expressed as the mean ± SD.
- A one-way ANOVA followed by Dunnett's multiple comparison test was used for the statistical analysis between the vehicle and drug-treated groups.
- Wilcoxon signed rank test was used to compare cystometric variables before and after treatment.
- For all statistical tests, $p<0.05$ was considered significant.

RESULTS

- Intravenous administration of ghrelin at 300, 600, and 900 µg/kg increased intercontraction intervals (ICI) in a dose-dependent fashion ($p<0.05$). These inhibitory effects were seen immediately after administration and returned to the pre-control level within 80 minutes.
- Intravenous administration of ghrelin at 300, 600, and 900 µg/kg also increased threshold pressure (TP) in a dose-dependent ($p<0.05$).
- There were no significant changes in maximum pressure (MP), basal pressure (BP) at any doses tested.
- When naloxone was administered one voiding cycle before ghrelin administration, the increases in ICI and TP induced by ghrelin administration alone were not seen.

Table 1. Changes in cystometric parameters after intravenous ghrelin administration in urethane-anesthetized rats

Variable	Vehicle	ghrelin (300 µg/kg)	ghrelin (600 µg/kg)	ghrelin (900 µg/kg)	naloxone (3 mg/kg) and ghrelin (900 µg/kg)
Number of rats	6	6	6	6	6
Mean ± SD					
%ICI, %	101.5 ± 5.8	119.1 ± 3.8†	147.5 ± 8.3†	154.4 ± 11.5†	103.2 ± 3.2
BP, cmH_20					
before	2.78 ± 0.51	2.61 ± 0.89	3.05 ± 1.01	2.12 ± 1.27	3.01 ± 0.87
after	2.85 ± 1.12	3.21 ± 0.91	2.94 ± 0.67	3.31 ± 0.99	3.18 ± 1.02
TP, cmH_20					
before	6.02 ± 2.15	5.54 ± 0.89	5.31 ± 1.54	5.98 ± 1.07	5.13 ± 2.71
after	4.75 ± 1.87	9.58 ± 1.03*†	12.7 ± 1.51*†	15.6 ± 3.11*†	5.69 ± 2.51
MP, cmH_20					
before	27.3 ± 5.21	32.1 ± 7.12	29.6 ± 4.12	30.5 ± 6.71	35.1 ± 8.15
after	26.1 ± 3.41	33.7 ± 9.78	32.1 ± 9.91	31.8 ± 9.21	30.5 ± 10.6

* P <0.05 (*paired t-test*), † P <0.05 vs vehicle injection (Dunnett's multiple comparison test)

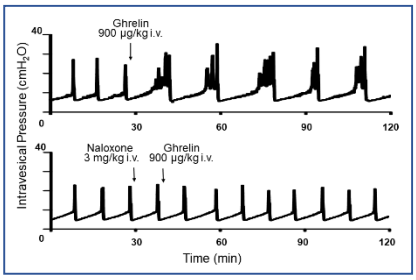

Fig. 1. Effects of intravenous administration of ghrelin and naloxone on bladder activity in urethane-anesthetized rats. Arrows indicate drug administration.

DISCUSSION

- The main function of ghrelin seems to be mediated by modulation of afferent activity because ghrelin induced increases in ICI and TP without affecting MP or BP.
- In addition, because the ghrelin-induced increases in ICI and TP were prevented when naloxone was administered prior to ghrelin application, indicating that the effects of ghrelin were mediated by activation of the opioid system.

CONCLUSIONS

- These results in this study indicate that ghrelin plays an important role in the control of the micturition reflex and that ghrelin can inhibit the micturition reflex through activation the opioid system.

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Disclosures Statement

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