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PERIPHERAL GHRELIN ADMINISTRATION INCREASES BLADDER CAPACITY WITHOUT AFFECTING THE BLADDER CONTRACTION PRESSURE OR ELECTROENCEPHALOGRAM IN RATS

Hypothesis / aims of study

We have investigated the association of sleep disturbance and nocturia. We previously reported that melatonin, a modifier of the circadian rhythm, increased bladder capacity (BC) [1]. It has been known that ghrelin induces slow-wave sleep via the secretion of the growth hormone (GH). Recently, it has been suggested that ghrelin inhibits the contraction of bladder strips *in vitro* [2]. Thus, we hypothesized that ghrelin could alleviate both sleep disturbance and nocturia. In the present study, we investigated the effects of ghrelin on sleep and bladder functions.

Study design, materials and methods

Eleven female Sprague-Dawley rats (weighing 200-220 g) were used. To evaluate the effects of ghrelin on bladder function, continuous cystometric recordings were obtained. In study 1, ghrelin was administered into the left lateral ventricle to investigate its central effect. In study 2, ghrelin was administered into the jugular vein during continuous electro-encephalogram (EEG) recording. To record the EEG, we surgically placed silver ball electrodes in contact with the pia mater of the rat. All measurements were performed after the recovery from anesthesia and operation. Ghrelin was dissolved in distilled water, and the concentration was adjusted by physiological saline. The injection volumes of intracerebroventricular (icv) and intravenous (iv) drug administration were 5 µl and 0.1 ml, respectively. The EEG data are expressed with the power value of the delta wave. The results are presented as means ± standard error. Statistical comparisons were performed by ANOVA followed by the Dunnett test.

Results

Six and 5 rats were enrolled in study 1 and 2, respectively. Ghrelin icv administration (from 10 nM to 100 µM) had no significant effect on bladder capacity (Figure 1a) or bladder contraction pressure (BCP: Figure 1b). Ghrelin iv administration significantly increased BC dose-dependently by 97.8 %, 126.1 %, 145.7 % at 1, 10 and 100 µM, respectively (Figure 2a). However, ghrelin iv administration showed no significant effect on BCP or EEG readings at any dose (Figure 2b and 3).

Interpretation of results

The effects of ghrelin on smooth-muscle contraction have been controversial. Ghrelin stimulates the motility of the digestive tract; alternatively it has a relaxation effect on the smooth muscle of the vasculature. Our results suggest that ghrelin increases the BC of rats as a peripheral effect. Tolekova et al. also showed that ghrelin inhibited angiotensin-2 and vasopressin induced bladder contraction [2]. With respect to the mechanism of detrusor relaxation, they supposed an association with the cAMP. The delta wave in the EEG is typically seen during slow-wave sleep. Our results show no increase of slow wave sleep after ghrelin administration. Since we carried out the measurement in the daytime, ghrelin was supposed not to stimulate the secretion of GH effectively.

Concluding message

In the present study, the administration of ghrelin showed no effect on EEG results. However, our results suggest that ghrelin increases BC by peripheral action. To our knowledge, this is the first *in vivo* study concerning the effect of ghrelin on bladder function. Further studies are required to elucidate the exact effect of ghrelin on the bladder function.

Figure 1a

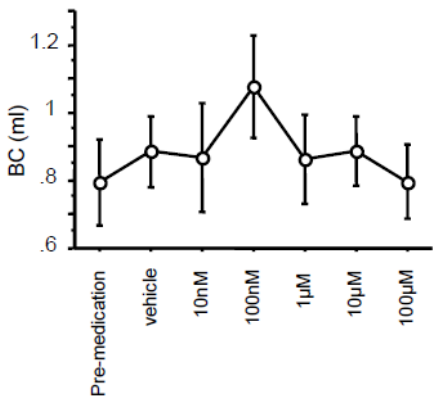


Figure 1b

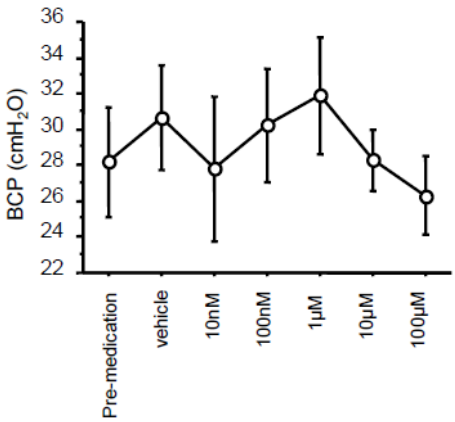


Figure 2a

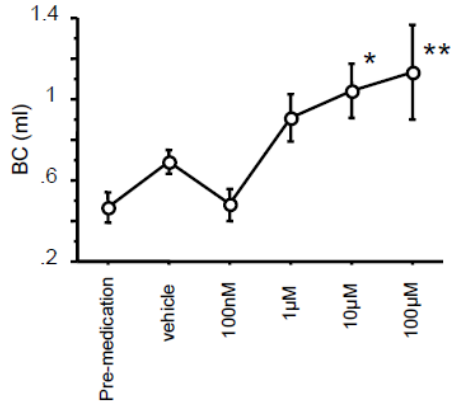
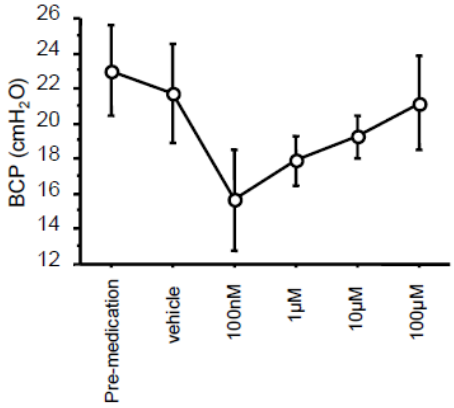
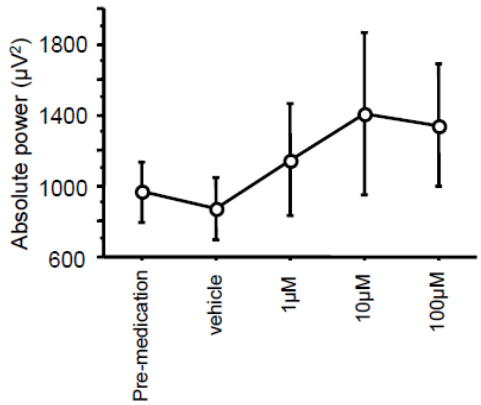


Figure 2b



Single asterisk indicates pre-medication vs vehicle or ghrelin ANOVA (Dunnett) p <0.05.
Double asterisks indicates pre-medication vs vehicle or ghrelin ANOVA (Dunnett) p <0.01

Figure 3



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2. Tolekova AN, Hadzhibozheva PV, Iliev RN, Georgiev CK, Trifonova KY, Sandeva RV, Kalfin RE and Ilieva GS. Participation of extracellular Ca2+ or ghrelin in peptide-mediated contraction of strips from urinary bladder. Regul Pept 2010; 162: 79-83.

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**the Animal Care and Use Comittee of the University of Fukui**