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Miwa Y[1], Kaneda T[1], Akino H[1], Yokoyama O[1]
1. Department of Urology, Faculty of Medical Science, University of Fukui

EFFECTS OF CORTICOTROPIN-RELEASING FACTOR RECEPTOR ANTAGONISTS ON BLADDER OVERACTIVITY INDUCED BY PSYCHOLOGICAL STRESS IN RATS

Hypothesis / aims of study

Corticotropin-releasing factor (CRF) coordinates the neural, endocrine and immune responses of the body to stress. Therefore, CRF receptors are important targets for the design of drugs for stress-related disorders. Epidemiological studies reveal a significant correlation between anxiety and voiding disorders. Psychological stress aggravates symptoms in interstitial cystitis and overactive bladder syndrome. The aim of this study was to investigate the alterations in micturition in response to psychological stress in rats and to investigate the effects of CRF receptor antagonists on bladder function.

Study design, materials and methods

Spontaneous Hypertensive Rats (8 weeks old) were used as experimental subjects.

First the rats were randomly assigned to control and psychological stress groups. Psychological stress was induced by the communication box for 2 hours. Control group rats were exposed to clean and empty cages for the same period. After the stress loading, each rat was placed in a metabolic cage for 3 hours to assess voided volume per micturition and voiding frequency.

Secondly the rats were intraperitoneally (i.p.) injected with vehicle, astressin (100μg), non selective CRF receptor (CRF-R1/R2) antagonist, or NBI-27914 (100μg), CRF receptor type 1 (CRF-R1) antagonist and 10 min later were exposed to psychological stressed for 2 hours. After the stress loading, voiding behaviour was observed in a metabolic cage.

Thirdly cystometrography in conscious rats was performed. Insertion of a polyethylene catheter through the bladder dome was performed using halothane anaesthesia. We investigated the effects of astressin (10 or 100μg) or NBI-27914 (10, 50 or 100μg) on micturition reflex. Each drug was administered via intracerebroventricular or intravenous routes. Two cystometric parameters (bladder contraction interval and bladder contraction pressure) were determined from each cystometry.

Results

Voided volume per micturition was significantly reduced and voiding frequency was significantly increased in psychologically stressed group compared with control group ($p<0.05$). Pretreatment with intraperitoneal astressin significantly increased voided volume per micturition in stressed group ($p<0.05$), but pretreatment with NBI-27914 had no significant effect on voiding behaviour in stressed group. Bladder contraction interval was significantly increased after intravenous administration of astressin compared with the vehicle group ($p=0.02$). NBI-27914 had no significant effect on contraction interval. No significant differences in bladder contraction pressure were found between CRF receptor antagonists and vehicle.

Interpretation of results

Our results suggest that the micturition reflex in rats could be enhanced under psychological stress induced by the communication box and are compatible with the fact that patients with interstitial cystitis and overactive bladder syndrome display symptom aggravation after exposure to psychological stress. Two major G-protein coupled receptors for the mammalian neuropeptide CRF have been identified as CRF-R1 and CRF-R2. In rodent, CRF-R1 mRNA is primarily expressed in the pituitary, cerebral cortex, amygdala and hippocampus, and CRF-R2 mRNA is predominantly expressed in peripheral tissues (e.g., cardiac myocytes, gastrointestinal tract, lungs, ovaries and urinary bladder). We showed that CRF-R1/R2 antagonist, but not CRF-R1 antagonist, administered via intravenous or intraperitoneal inhibited the micturition reflex. It is possible that peripheral CRF-R2 is involved in the micturition threshold in rats. Further studies are needed to verify this point.

Concluding message

We investigated the alterations in micturition in response to psychological stress and the effects of CRF receptor antagonists on bladder function in rats. Voiding behaviour in rats was enhanced under psychological stress induced by the communication box. Our results suggest that peripheral CRF-R2 could be involved in the micturition threshold in rats. However, species differences in receptor subtype density in the central nervous system or periphery should be considered. These data provide rationale for further study and development of CRF receptor antagonists as novel agents in the treatment of interstitial cystitis and overactive bladder syndrome.

References

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