WATER AVOIDANCE STRESS INDUCED BLADDER OVERACTIVITY IN MICE IS ASSOCIATED WITH ENHANCED CONTRACTILE BLADDER RESPONSES

#133

WEST, E. G., SELLERS, D., CHESS-WILLIAMS, R., MCDERMOTT, C.
Centre for Urology Research, Bond University, Gold Coast, Australia

INTRODUCTION

Bladder dysfunction such as overactive bladder, incontinence and interstitial cystitis are common in the general population and even more common with age (Teleman et al., 2004). A body of clinical evidence exists linking bladder disorders with stress, anxiety and depression, including witness trauma (Lai, 2015). Stress appears to greatly influence the development of bladder symptoms, or worsens symptom severity (Minassian, Devore, Hagan, & Grodstein, 2013). In spite of this, there is little research on the precise changes and underlying mechanisms.

This study investigates the hypothesis that water avoidance stress in mice causes bladder dysfunction and an overactive bladder phenotype via mechanisms including altered detrusor responses.

METHODS

Female C57BL/6J mice (12-14 weeks) were randomly allocated to Control (n=5) or Water Avoidance Stress (WAS) (Stress) (n=5) experimental groups. WAS mice were placed on a central pedestal surrounded by room temperature distilled water for 1hr/day for 10 days. Controls were age-matched and housed normally without environmental stress exposure. Voiding pattern analysis was performed prior to (Day 0) and on days 1, 3, 5, 7 and 10 of the stress protocol. Mice were euthanised 24 hours after the final stress exposure and bladders were removed and an isolated bladder preparation methodology was taken from previous studies by our group (West et al., 2018).

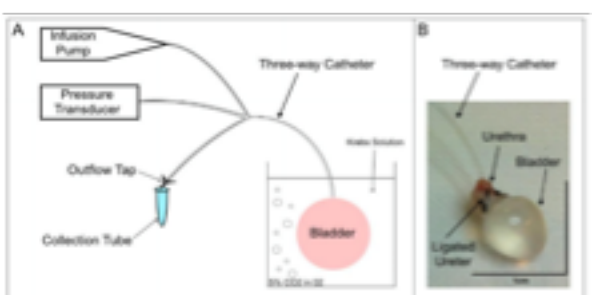

Figure 1: (A) Schematic displaying the isolated whole bladder set up. (B) Photograph of whole bladder preparation attached to three-way catheter.

The bladders were catheterised **(Figure 1)** and intravesical pressure responses recorded during distension with saline and in response to stimulation using carbachol, ATP, isoprenaline, KCl and electrical field stimulation (EFS).

CONCLUSIONS

Repeated exposure to environmental stress through water avoidance altered voiding behaviour and enhanced contractile bladder responses to muscarinic and purinergic stimulation. In addition, the contribution of neuronal ATP to efferent nerve evoked contractile responses increased respectively in bladders from WAS mice.

Environmental stress causes an overactive bladder phenotype. The mechanism involved appears to include enhanced responsiveness of the detrusor muscle to muscarinic and purinergic stimulation.

RESULTS

Stress induced an overactive bladder phenotype in mice with a significant increase in the number of voiding events observed at all time points tested **(Figure 2)**. Urinary frequency doubled by 24-hours following the first stress exposure ($p<0.05$) and increased 7-fold ($p<0.001$) following 10-days WAS. This increase in frequency was associated with a significant decrease in void size but no change in total voided volume (data not shown).

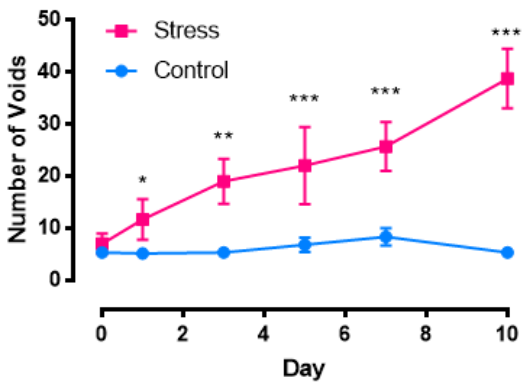

***Figure 2**: Number of voids over a 4-hour period during voiding pattern analysis in control and stress mice. Data represents mean ± SEM (n=5). * vs control*

Contractile responses to the muscarinc agonist carbachol ($p<0.05$) **(Figure 3A)**, and purinergic agonists ATP ($p<0.05$) and alpha,beta-mATP ($p<0.05$) **(Figure 3B)** were significantly increased in bladders from WAS mice, with no significant change in response to KCl (data not shown).

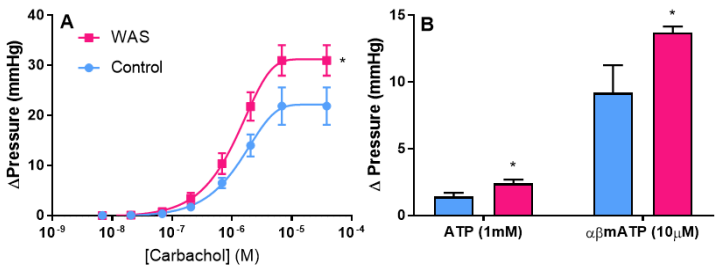

***Figure 3**: Contractile responses to (A) muscarinic stimulation with carbachol and (B) purinergic stimulation in bladders from control and stress mice. Data represents mean ±SEM (n=5).*

Bladder pressure responses to EFS were not altered by stress **(Figure 4A)**. Purinergic receptor desensitisation using αβ mATP reduced responses to EFS more in bladders from stress mice (65.9 ± 2.0%) than control mice (50.5 ± 2.4%) **(Figure 4B)**. Atropine reduced neurogenic contractions similarly in both control and stress bladders.

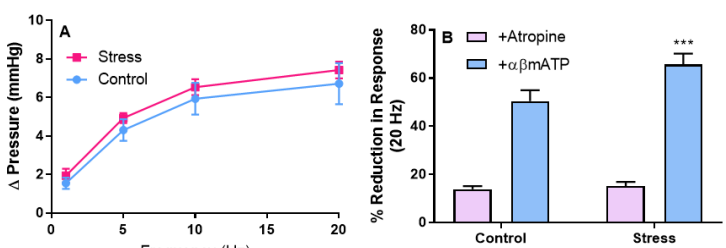

***Figure 4**: Contractile responses to (A) electric field stimulation (EFS) and (B) reduction in response to EFS (20Hz) in the presence of atropine and αβ mATP in bladders from control and stress mice. Data represents mean ±SEM (n=5).*

REFERENCES

Teleman, P. M., Lidfeldt, J., Nerbrand, C., Samsioe, G., Mattiasson, A., & group, W. s. (2004). Overactive bladder: prevalence, risk factors and relation to stress incontinence in middle-aged women. *BJOG, 111*(6), 600-604. doi:10.1111/j.1471-0528.2004.00137.x. Lai, H., ; Gardner, V., Vetter, J. & Andriole, G.L. (2015). Correlation between psychological stress levels and the severity of overactive bladder symptoms. *BMC Urology, 15*(14). doi:10.1186/s12894-015-0009-6. Minassian, V. A., Devore, E., Hagan, K., & Grodstein, F. (2013). Severity of urinary incontinence and effect on quality of life in women by incontinence type. *Obstet Gynecol, 121*(5), 1083-1090. doi:10.1097/AOG.0b013e31828ca761. West, E. G., Lang, R., Sellers, D., Chess-Williams, R., & McDermott, C. (2018). Ibuprofen Decreases Spontaneous Activity and Enhances Nerve-Evoked Contractions to Minimize Mitomycin C-Induced Bladder Dysfunction. *J Pharmacol Exp Ther, 366*(2), 282-290. doi:10.1124/jpet.118.248989. Farr, S. E., Chess-Williams, R., & McDermott, C. M. (2017). Gemcitabine: Selective cytotoxicity, induction of inflammation and effects on urothelial function. *Toxicol Appl Pharmacol, 316*, 1-9. doi:10.1016/j.taap.2016.12.011.