

# Impact of psychological stress on bladder function is dependent on type of stress.



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## INTRODUCTION

A body of clinical evidence has linked psychological stress with bladder disorders, including post-traumatic stress disorder and witness trauma (Mann, et al., 2015). Stress appears to cause or worsen the symptoms of bladder dysfunction with around 40% of people reporting poor outcomes from current treatments (Arrabal-Polo, et al., 2012). Many bladder disorders have been associated with voiding dysfunction, particularly in people with a history of abuse. Several rodent models of psychological stress have been used to investigate changes in bladder function (West, et al., 2018), however, to date no studies have investigated if voiding dysfunction occurs in models of witness trauma. The aim of this study was to determine the effects of stress, caused by social defeat or witness trauma, on voiding behaviour and bladder function using in vivo voiding pattern analysis and an ex vivo bladder preparation.

## METHODS

Male ex-breeder Male C57Bl/6J mice (12-14 weeks) pairs were randomly allocated to either the 1) social defeat or 2) witness trauma experimental group. C57Bl/6J pairs were placed in a plexiglass chamber with an aggressor ARC1 mouse for 1 hour/day for 10 days (Fig. 1). Control pairs were housed under normal conditions for the duration of the study. Voiding pattern analysis was conducted on days 0, 1, 3, 5, 7 and 10. Mice were euthanised 24-hours after final stress exposure and a blood sample was taken for analysis of corticosterone. Bladders were then removed, catheterised and intravesical pressure responses recorded during distension and in response to stimulation of purinergic and cholinergic agonists, and following electrical field stimulation (Fig. 2).

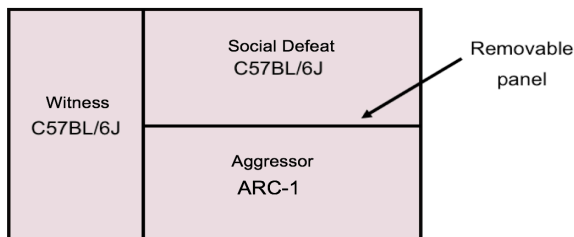


Figure 1: Diagram of social defeat and witness trauma chamber.

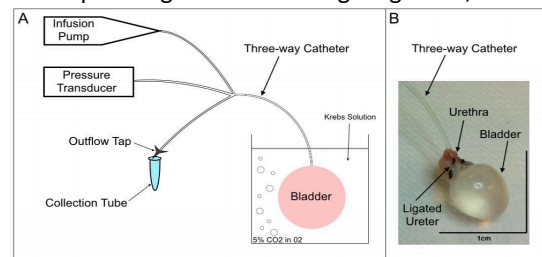


Figure 2: (A) Schematic displaying the three-way catheter set up. (B) Whole bladder preparation attached to three-way catheter. (Farr, Chess-Williams, & McDermott, 2017)

## RESULTS

Plasma corticosterone levels were significantly increased following 10-days of social defeat or witness trauma stress when compared to unstressed controls ( $p < 0.001$ ) (Fig. 3A). Voiding pattern analysis revealed no significant difference in total voided volume between groups; however, a significant increase in the average void size was observed in the social defeat group from day 3 compared to unstressed control animals (Fig. 1B), indicating an altered voiding phenotype. Witness trauma did not alter voiding behaviour at any timepoint tested.

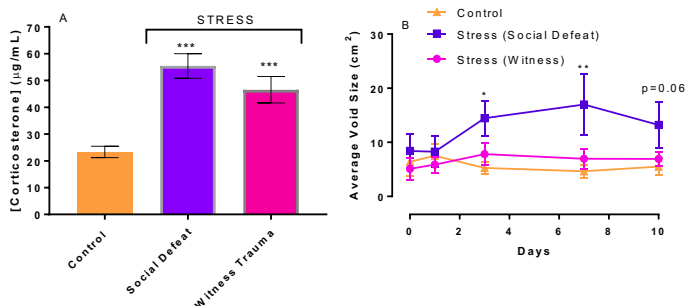


Figure 3: Effect of psychological stress caused by social defeat or witness trauma on plasma corticosterone (A), and average void size (B).  $n \geq 6$ , mean  $\pm$  SEM, \*vs controls.

Contractile response to carbachol and KCl was not altered in either stress group, nor was relaxation to the beta-adrenoceptor agonist isoprenaline. However, pressure response to the purinergic agonist  $\alpha\beta$ mATP was significantly increased by social defeat but not witness trauma (Fig. 4A). Similarly nerve evoked contractile responses to EFS were significantly increased at all frequencies in bladders from social defeat but not witness trauma mice (Fig. 4B).

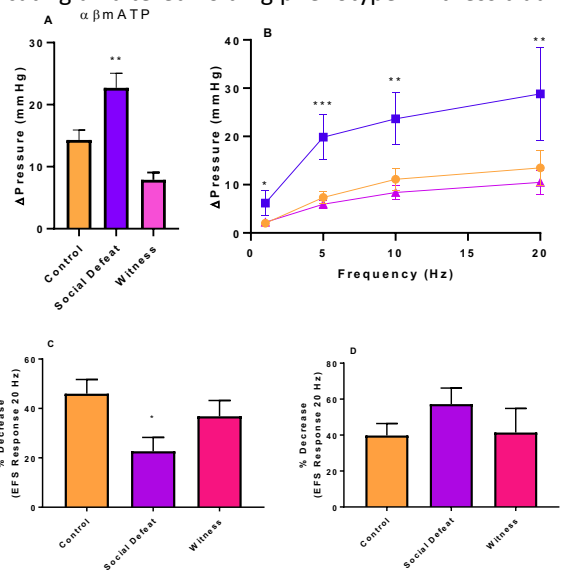


Figure 4: Effect of psychological stress caused by social defeat or witness trauma on A) contractile response to  $\alpha\beta$ mATP, B) response to electric field stimulation, and % decrease in EFS response in the presence of atropine C) or following desensitization of purinergic receptors with  $\alpha\beta$ mATP (D).  $n \geq 6$ , mean  $\pm$  SEM, \*vs controls.

## CONCLUSIONS

Exposure to physical or emotional stress produces a similar hormonal stress response in both models of stress (social defeat and witness trauma). However, the changes in voiding behaviour and local functional changes in the bladder appear to be dependent on the type of stressor. The increase in average void size observed in the social defeat group is consistent with previous reports of urine retention in this model when using male mice. This is in contrast to the increased voiding frequency and decreased average void size which we have observed in female mice following water avoidance stress (West, et al., 2018). The increase in contractility to EFS and  $\alpha\beta$ mATP, may indicate a change in responsiveness of the purinergic system. Stress induced functional bladder changes are dependent on stressor type. This study reports a male model of social defeat with reduced urinary frequency, with no voiding changes observed in the witness.

## REFERENCES

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