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# Acute hypernatremia dampens stress-induced enhancement of long-term potentiation in the dentate gyrus of rat hippocampus

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**Summary** Stress often occurs within the context of homeostatic threat, requiring integration of physiological and psychological demands to trigger appropriate behavioral, autonomic and endocrine responses. However, the neural mechanism underlying stress integration remains elusive. Using an acute hypernatremic challenge (2.0 M NaCl subcutaneous), we assessed whether physical state may affect subsequent responsiveness to psychogenic stressors. We found that experienced forced swimming (FS, 15 min in 25 °C), a model of psychogenic stress, enhanced long-term potentiation (LTP) induction in the dentate gyrus (DG) of the rat hippocampus *ex vivo*. The effect of FS on LTP was prevented when the animals were adrenalectomized or given mineralocorticoid receptor antagonist RU28318 before experiencing stress. Intriguingly, relative to normonatremic controls, hypernatremic challenge effectively elevated plasma sodium concentration and dampened FS-induced enhancement of LTP, which was prevented by adrenalectomy. In addition, acute hypernatremic challenge resulted in increased extracellular signal-regulated kinase (ERK)1/2 phosphorylation in the DG and occluded the subsequent activation of ERK1/2 by FS. Moreover, stress response dampening effects by acute hypernatremic challenge remained intact in conditional oxytocin receptor knockout mice. These results suggest that acute hypernatremic challenge evokes a sustained increase in plasma corticosterone concentration,

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which in turn produces stress-like changes in the DG, thereby occluding subsequent responsiveness to psychogenetic stress. They also fit into the general concept of "metaplasticity" — that is, the responsiveness to stress is not fixed but appears to be governed by the recent history of prior physical state.


## 1. Introduction

Stress is a common experience in daily life. It initiates adaptive processes that allow the organism to physiologically cope with environmental perturbations in maintaining homeostasis and promoting survival (referred to as "allostasis") (Sterling and Eyer, 1981; McEwen, 1998, 2000). However, if individuals are not able to cope efficiently with stressors and cannot regain allostasis, the detrimental effects on psychological and physiological functions, termed "allostatic load", may occur (McEwen, 2000, 2002). Both allostasis and allostatic load operate in all body systems, especially the brain. The brain serves as the main coordinating center for interpreting, categorizing and responding to environmental challenges, and is a target of those challenges (McEwen, 2000). However, less is known about how the brain orchestrates adaptive responses to meet the demands imposed by stressors.

Stress can be either physical or psychological in nature. Physical stress is caused by a real or perceived physical threat that creates changes in the internal environment and perturbs body's homeostasis, whereas psychological stress is associated with psychogenic stressors that elicit strong emotional responses and interpret the external environmental stimuli as potential insults (Krause et al., 2011). Although arising from different origins, both forms of stress are similar in many ways and people frequently suffer from a combination of these two types of stress. This raises the question of whether physical and psychological stress may interact with each other. In this regard, a recent study has shown that an acute physical (hypernatremic) challenge significantly reduced hypothalamic—pituitary—adrenal (HPA), cardiovascular and behavioral responsiveness to subsequent physical restraint, a model of psychogenic stress (Krause et al., 2011). However, whether these acute hypernatremia-induced stress response dampening effects are specific to physical restraint or are generalized to other psychogenic stressors has not yet been determined.

Stress dramatically affects different forms of synaptic plasticity and memory processes in the hippocampus (Kim and Diamond, 2002; Huang et al., 2005; Schmidt et al., 2013). We and others have reported that, in the CA1 area of the hippocampus, a brief experience of acute restraint-tail shock stress can impair high-frequency stimulation (HFS)-induced long-term potentiation (LTP) (Shors et al., 1989; Diamond et al., 1992; Kim et al., 1996; Yang et al., 2004, 2006), whereas the induction of long-term depression (LTD) by prolonged low-frequency stimulation is facilitated (Kim et al., 1996; Xu et al., 1997; Yang et al., 2004, 2005). By contrast, brief neck restraint stress enhances LTP and impairs LTD in the dentate gyrus (DG) of mouse hippocampus (Spyrka et al., 2011). Stress-induced modifications in synaptic plasticity could therefore represent a useful model to examine whether physical state affects subsequent responsiveness to psychogenic stressors. In this study, we examined the impact of an acute hypernatremic challenge on subsequent forced swimming (FS)-induced modification of LTP maintenance in the DG of rat or mouse hippocampal slices. Our findings confirm that physical and psychogenic stressors activate overlapping neural mechanisms to alter physiological processes, and provide novel evidence for occluded responsiveness to subsequent psychogenic stressors by an acute physical challenge.

## 2. Material and methods

### 2.1. Animals and handling

Male adult Sprague-Dawley rats (8—10 weeks old) or C57BL/6J mice (8—10 weeks old) were used in these experiments. Rats were originally imported from Charles River Laboratories (Wilmington, MA) and were bred in our animal facilities. Homozygous oxytocin receptor (OXTR)-floxed ($Oxtr^{tm1.1Wsy}$/J) and calmodulin-kinase II (CamK)-cre transgenic mice were originally obtained from The Jackson Laboratory (Bar Harbor, ME), and bred within our animal facility. $Oxtr^{tm1.1Wsy}$/J mice were crossed to CamK-cre mice to generate conditional OXTR knockout mice. Mice were genotyped by a PCR-based method using genomic DNA isolated from tail samples. The knockout mice were backcrossed to C57BL/6J mice for 5 generations to obtain a homogeneous genetic background. Animals were housed in groups of three in a humidity- and temperature-controlled (25 ± 1 °C) vivarium on a 12 h light/dark cycle with access to food and water *ad libitum*. All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of National Cheng Kung University.

### 2.2. Adrenalectomy and corticosterone replacement

Adrenalectomy (ADX) was performed *via* small bilateral dorsal flank incisions under isoflurane anesthesia as described previously (Chen et al., 2010). ADX rats received replacement corticosterone (10 μg/ml) in drinking water containing 0.9% saline immediately after surgery. Rats were used for experiments 2 weeks after surgery. Control rats underwent the same surgical procedure as the ADX rats, except that adrenal glands were not removed. Successful ADX was verified by measuring plasma corticosterone levels.