

MEETING ABSTRACT

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# Modulation of magnesium deficiency-induced anxiety and HPA axis dysregulation by therapeutic drug treatment

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## Background

Preclinical and some clinical studies suggest a relationship between perturbation in magnesium homeostasis and pathological anxiety, although the underlying mechanisms remain largely unknown. Since there is evidence that  $Mg^{2+}$  modulates the hypothalamic-pituitary-adrenal (HPA) axis, we tested whether enhanced anxiety-like behaviour can be reliably elicited by dietary  $Mg^{2+}$  restriction and whether  $Mg^{2+}$  deficiency is associated with altered HPA axis function.

## Methods

Mice assigned to  $Mg^{2+}$ -deficient groups were allowed to freely access a 0.005%  $Mg^{2+}$ -containing diet while control mice were fed a normal, 0.2%  $Mg^{2+}$ -containing diet. The emotional behaviour of  $Mg^{2+}$ -deficient mice was assessed in a battery of anxiety tests including the open field test, the light/dark test, the stress-induced hypothermia test, and the hyponeophagia test. Markers of HPA axis function including CRH gene expression and plasma ACTH levels were quantified. Neuronal activation patterns in the HPA system were investigated using mapping of the immediate early gene *c-Fos* as a marker of neuronal activation in response to an anxiety-provoking situation.

## Results

Compared to controls,  $Mg^{2+}$ -deficient mice did indeed display enhanced anxiety-related behaviour in numerous anxiety tests. The enhanced anxiety-related behaviour of

$Mg^{2+}$ -deficient mice was sensitive to chronic desipramine treatment in the hyponeophagia test and to acute diazepam treatment in the open arm exposure test.  $Mg^{2+}$  deficiency caused an increase in the transcription of corticotropin releasing hormone in the paraventricular hypothalamic nucleus (PVN), which coincided with elevated ACTH plasma levels, pointing to an enhanced set-point of the HPA axis. Chronic treatment with desipramine reversed the identified abnormalities of the stress axis. Functional mapping of neuronal activity revealed hyper-excitability in the PVN of anxious  $Mg^{2+}$ -deficient mice and its normalisation through diazepam treatment.

## Conclusions

Overall, the present findings demonstrate the robustness and validity of the  $Mg^{2+}$  deficiency model as a mouse model of enhanced anxiety, showing sensitivity to treatment with anxiolytics and antidepressants. It is further suggested that dysregulations in the HPA axis may contribute to the hyper-emotionality in response to dietary induced hypomagnesaemia.

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