J Physiol 596.10 (2018) pp 1781–1782

The Journal of Physiology

PERSPECTIVES

The relationship between GABA and stress: 'it's complicated'

Jamie Maguire
Neuroscience Department, Tufts University School of Medicine, Boston, MA, USA
Email: jamie.maguire@tufts.edu

Edited by: Ian Forsythe & Maike Glitsch

GABA is well known to be a critical regulator of the body's physiological response to stress through tight regulation of hypothalamic–pituitary–adrenal (HPA) axis function (Cullinan *et al.* 2008). Nearly half of the synapses onto corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN), which govern the activity of the HPA axis, are GABAergic. CRH neurons have been shown to be regulated by both phasic and tonic GABAergic inhibition, which are distinct types of GABAergic inhibition mediated by specific subtypes of $GABA_A$ receptors ($GABA_A$Rs) with unique pharmacological properties and subcellular distribution. Despite the well-accepted role for GABA in the regulation of the HPA axis, few laboratories have investigated the functional contribution of GABAergic signalling and plasticity on CRH neuronal activity and HPA axis function. In fact, many of the synaptic mechanisms regulating the HPA axis have only recently been elucidated (Levy & Tasker, 2012), and the authors of the article that this Perspective highlights have contributed considerably to our knowledge on this topic (Bains *et al.* 2015).

The negative feedback of glucocorticoids, including corticosterone (CORT), is well established in the regulation of the HPA axis involving actions on glucocorticoid receptors on CRH neurons. The article in this issue of *The Journal of Physiology* by Colmers & Bains (2018) further examines the effects of CORT on diverse GABAergic mechanisms regulating CRH neurons. The authors demonstrate that CORT alters GABAergic signalling through changes in the expression of postsynaptic $GABA_A$Rs and tonic GABAergic inhibition. The authors also expose that GABAergic control of CRH neurons is constitutively under suppression through actions on presynaptic $GABA_B$ receptors, thereby minimizing GABA release, which can be enhanced by blockade of GABA transporters (GATs). Further, this study also demonstrates that GATs suppress the activation of extrasynaptic $GABA_A$Rs, limiting tonic GABAergic control of CRH neurons, which can be unmasked by blocking GATs. These data demonstrate that CRH neurons are regulated by both tonic and phasic GABAergic inhibition, although the magnitude of these different types of inhibition may be modified by the extent of GAT function and/or the presence of CORT. Thus, this study demonstrates three separate GABAergic mechanisms controlling the activity of CRH neurons in the PVN: GAT-mediated influence on presynaptic $GABA_B$ receptors, GAT regulation of tonic GABAergic inhibition, and CORT-mediated postsynaptic $GABA_A$R regulation.

Although the mechanisms of corticosterone-mediated regulation of $GABA_A$Rs in this context are unknown, a neuroactive derivative of corticosterone, THDOC, has been shown to regulate the expression of $GABA_A$Rs via phosphorylation of specific $GABA_A$R subunits (Abramian *et al.* 2014). Interestingly, similar mechanisms have been also shown for other steroid hormones, including ovarian hormones and their neurosteroid derivatives, such as allopregnanolone (Modgil *et al.* 2017). Thus, there is the potential for ovarian hormone-mediated changes in $GABA_A$Rs in CRH neurons, which may also impact the regulation of CRH neurons and, thus, the HPA axis. Further studies are required to investigate this potential novel mechanism linking ovarian and stress hormones. Consistent with an interaction between ovarian hormones and stress, altered stress reactivity and vulnerability to mood disorders have been demonstrated over the oestrous cycle (MacKenzie & Maguire, 2014). It is tempting to speculate that the oestrous cycle-linked changes in stress reactivity may involve changes in the GABAergic control of CRH neurons, similar to the CORT observations described here, given the evidence for alterations in $GABA_A$R subunit expression over the oestrous cycle in other brain regions (MacKenzie & Maguire, 2014).

The evidence that GATs limit presynaptic $GABA_B$-mediated reduction in GABA release, thereby facilitating GABAergic signalling, whereas, they prevent extrasynaptic $GABA_A$R-mediated tonic inhibition postsynaptically, by limiting the concentration of GABA reaching these receptors, suggests that GATs perform a unique function in balancing tonic and phasic GABAergic inhibition. Further, data presented in Colmers & Bains (2018) demonstrate that presynaptic $GABA_B$ receptors are constitutively active on presynaptic terminals impinging on CRH neurons in the PVN. These findings suggest that at baseline GAT function is incapable of completely limiting $GABA_B$-mediated suppression of GABA release. However, the authors also demonstrate a lack of tonic current at baseline, which is only unmasked after GAT inhibition. Therefore, it appears that at baseline GAT function allows some degree of presynaptic $GABA_B$ signalling but not actions on extrasynaptic $GABA_A$Rs which mediate tonic inhibition. This may be due to the localization of GATs in relation to presynaptic $GABA_B$ receptors and extrasynaptic $GABA_A$Rs. Either way, these findings reveal a novel mechanism and unique tuning of the GABAergic control of CRH neurons, which may be further influenced by stress.

The physiological relevance of these CORT-mediated regulatory mechanisms controlling CRH neurons remains to be fully explored. For example, how does this mechanism influence stress reactivity? It is reasonable to assume that these changes, such as the CORT-mediated increase in tonic GABAergic inhibition of CRH neurons, would provide a novel negative feedback onto the HPA axis. However, evidence of the stress-induced collapse of the chloride gradient and compromised GABAergic inhibition (Hewitt *et al.* 2009; Sarkar *et al.* 2011) add further complexity to the role of GABAergic control of the HPA axis and stress reactivity. In addition to the potential effects of stress-induced CORT on $GABA_A$R regulation, the effects of stress on GAT expression and/or function remains to be determined. Very few studies have investigated changes in GABA uptake associated with stress, which this study suggests may have profound effects on HPA axis function.

Previous studies have demonstrated stress-induced changes in the GABAergic

DOI: 10.1113/JP275937

regulation of CRH neurons, including altered $GABA_AR$ subunit expression, a reduction in presynaptic GABA release, and overall impairments in GABAergic signalling onto CRH neurons (Herman & Tasker, 2016). The CORT-mediated effects on the GABAergic regulation of CRH neurons demonstrated in Colmers & Bains (2018) may contribute to these stress-induced changes in GABAergic regulation of CRH neurons. Future studies are required to fully appreciate the roles of stress and CORT in the GABAergic regulation of CRH neurons and the HPA axis, but this highlighted study takes a huge step in furthering our knowledge regarding the complicated relationship between GABA and stress.

References

Abramian AM, Comenencia-Ortiz E, Modgil A, Vien TN, Nakamura Y, Moore YE, Maguire JL, Terunuma M, Davies PA & Moss SJ (2014). Neurosteroids promote phosphorylation and membrane insertion of extrasynaptic $GABA_A$ receptors. *Proc Natl Acad Sci USA* **111**, 7132–7137.

Bains JS, Wamsteeker Cusulin JI & Inoue W (2015). Stress-related synaptic plasticity in the hypothalamus. *Nat Rev Neurosci* **16**, 377–388.

Colmers PLW & Bains JS (2018). Balancing tonic and phasic inhibition in hypothalamic corticotropin releasing hormone neurons. *J Physiol* **596**, 1919–1929.

Cullinan WE, Ziegler DR & Herman JP (2008). Functional role of local GABAergic influences on the HPA axis. *Brain Struct Funct* **213**, 63–72.

Herman JP & Tasker JG (2016). Paraventricular hypothalamic mechanisms of chronic stress adaptation. *Front Endocrinol* **7**, 137.

Hewitt SA, Wamsteeker JI, Kurz EU & Bains JS (2009). Altered chloride homeostasis removes synaptic inhibitory constraint of the stress axis. *Nat Neurosci* **12**, 438.

Levy BH & Tasker JG (2012). Synaptic regulation of the hypothalamic-pituitary-adrenal axis and its modulation by glucocorticoids and stress. *Front Cell Neurosci* **6**, 24.

MacKenzie G & Maguire J (2014). The role of ovarian hormone-derived neurosteroids on the regulation of $GABA_A$ receptors in affective disorders. *Psychopharmacology (Berl)* **231**, 3333–3342.

Modgil A, Parakala ML, Ackley MA, Doherty JJ, Moss SJ & Davies PA (2017). Endogenous and synthetic neuroactive steroids evoke sustained increases in the efficacy of GABAergic inhibition via a protein kinase C-dependent mechanism. *Neuropharmacology* **113**, 314–322.

Sarkar J, Wakefield S, MacKenzie G, Moss SJ & Maguire J (2011). Neurosteroidogenesis is required for the physiological response to stress: role of neurosteroid-sensitive GABA(A) receptors. *J Neurosci* **31**, 18198–18210.

Additional information

Competing interests

The author serves on the Scientific Advisory Board for SAGE Therapeutics.

Funding

The author is funded by NIH National Institute of Neurological Disorders and Stroke (NS102937).