

Evidence to Support The Non-Genomic Modulation of The HPA Axis

Anthony C. Johnson* and Beverley Greenwood-Van Meerveld

Oklahoma Center for Neuroscience, VA Medical Center, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, USA

The canonical targets for steroid hormones are cytosolic nuclear receptors that function to change cellular processes, over hours or days, through modification of gene transcription, which is considered a genomic effect [1]. However, controversy in the literature exists from studies that have demonstrated rapid, non-genomic (transcription independent) effects of steroid hormones [2]. The purpose of this editorial is to review the evidence supporting a role for non-genomic effects of the stress hormone corticosterone in the body's response to stress.

Anything that causes a deviation from homeostasis can be considered a stressor. However, if the stressor is due to an actual or perceived threat to one's well-being, the body responds by activating the sympathomedullary axis (the classical 'fight' or 'flight' response), the autonomic response, the hypothalamo-pituitary-adrenal (HPA) axis and the neuroendocrine response. The HPA axis is initiated by release of corticotropin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus (PVN) into the hypophyseal portal circulation to bind in the anterior pituitary. Adrenocorticotrophic hormone (ACTH) is then released from the pituitary into the systemic circulation to bind in the adrenal cortex to cause the synthesis and release of the glucocorticoid cortisol (corticosterone in rodents). Corticosterone then acts through feedback inhibitory mechanisms within the pituitary, PVN and limbic sites such as the hippocampus to terminate the HPA axis [3]. The inhibitory mechanisms are produced as the net result of binding to two distinct but related receptors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) [4,5].

Both GR and MR are members of the 3-ketosteroid nuclear receptor superfamily, which also includes progesterone and androgen receptors [6]. These receptors act as transcription factors, meaning that they reside in the cytoplasm in a complex of chaperone proteins and translocate to the nucleus after ligand binding. Corticosterone is an endogenous ligand for both receptors. MR, the high affinity receptor, is predominantly occupied under basal corticosterone secretion, in contrast to the lower affinity GR receptor which is only bound in response to stress-induced increases in plasma corticosterone [5,7]. Complexes of ligand-bound homo or heterodimers of GR and MR within the nucleus can directly bind to DNA and either initiate transcription if bound with co-activators or inhibit gene expression if bound with co-repressors [8,9]. While GR is ubiquitously expressed, MR expression is localized to discrete neuronal populations including the hippocampus and the hypothalamus [6]. Importantly, while these slow, genomic effects of GR and MR serve to modify long-term neuronal physiology, there is increasing evidence from electrophysiological studies for rapid, non-genomic effects of these receptors through putative membrane receptors in specific brain nuclei [10].

The effects of corticosterone on the electrophysiology of pyramidal neurons in the CA1 field of the hippocampus, a region that expresses both GR and MR, have been extensively investigated. Publications from the first ten years of research in this field indicated changes in the excitability of CA1 neurons in response to corticosterone application that supported a genomic mechanism of action, including a lack of change in membrane properties in the presence of the protein synthesis

inhibitor cyclohexamide and loss of calcium current increases in mice with a point mutation in their GR that prevented homodimerization [11,12]. Whereas more recent evidence for a non-genomic role of corticosterone was shown in cultured hippocampal neurons through the use of cell-impermeable corticosterone (bound to bovine serum albumin) that rapidly activated JNK and p38 signaling, which was insensitive to GR antagonism and blocked by a protein kinase C inhibitor [13]. In the same year, Karst et al. [14] demonstrated a role for membrane associated MR receptors, but not GR receptors, in the rapid effects of corticosterone on CA1 glutamatergic transmission using patch-clamp techniques in wild-type and tissue-specific GR or MR knock-out mice. To support the existence of membrane associated MR, electron microscopy was used to identify MR receptors at pre- and postsynaptic terminals within the lateral amygdala [15].

In contrast to the membrane MR that dictates the rapid response to corticosterone in the hippocampus, elegant electrophysiological, molecular and behavioral studies have demonstrated a role for membrane GR within the PVN. The initial study by Di et al. [16], used a combination of selective pharmacological tools, whole-cell recordings and single cell RT-PCR to build a model for rapid GR inhibition of parvocellular PVN neurons via retrograde endocannabinoid signaling to prevent glutamate release from the presynaptic terminals. A follow-up study by the same researchers in 2005 [17] demonstrated that not only do membrane GR cause rapid inhibition of glutamate release, but also facilitate the release of GABA in magnocellular PVN neurons, providing an additional mechanism to induce inhibition within the PVN. Concurrently, Johnson et al. [18] demonstrated the presence of membrane GR in pre- and postsynaptic terminals within the lateral amygdala, providing direct evidence for the existence of membrane GR. The in vivo functional consequences of the feedback inhibition model was shown through inhibition of plasma ACTH and plasma corticosterone responses to restraint stress in rats treated with cell-impermeable dexamethasone (a preferential GR agonist) and reversal of the inhibition with co-administration of a selective cannabinoid receptor inhibitor [19].

In summary, the classical genomic effects of GR and MR mediated by corticosterone are relevant to chronic changes in electrophysiological or morphological properties of neurons within the stress-axis. However, there is considerable evidence, that the rapid response to corticosterone is mediated by membrane GR/MR in a

***Corresponding author:** Beverley Greenwood-Van Meerveld, Oklahoma Center for Neuroscience, VA Medical Center, Research Admin. Rm. 151G, 921 N.E. 13th St. Oklahoma City, OK 73104, USA, Tel: 405-456-3547; Fax: 405-456-1719; E-mail: Beverley-Greenwood@ouhsc.edu

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nuclei specific manner. The functional consequences of this specific temporal regulation of the response to stress may have implications for behavioral disorders associated with abnormal cortisol regulation, such as depression, as well as inappropriate memory formation following stressful events, as occurs in post-traumatic stress disorder.

References

- McKenna NJ, O'Malley BW (2005) Teaching resources. An interactive course in nuclear receptor signaling: concepts and models. *Sci STKE* 2005: tr22.
- Hammes SR, Levin ER (2011) Minireview: Recent advances in extranuclear steroid receptor actions. *Endocrinology* 152: 4489-4495.
- Herman JP, Cullinan WE (1997) Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* 20: 78-84.
- Sapolsky RM, McEwen BS, Rainbow TC (1983) Quantitative autoradiography of [³H]corticosterone receptors in rat brain. *Brain Res* 271: 331-334.
- Reul JM, De Kloet ER (1985) Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology* 117: 2505-2511.
- Lu NZ, Wardell SE, Burnstein KL, Defranco D, Fuller PJ, et al (2006) International Union of Pharmacology. LXV. The pharmacology and classification of the nuclear receptor superfamily: glucocorticoid, mineralocorticoid, progesterone, and androgen receptors. *Pharmacol Rev* 58: 782-797.
- De Kloet ER, Reul JM (1987) Feedback action and tonic influence of corticosteroids on brain function: a concept arising from the heterogeneity of brain receptor systems. *Psychoneuroendocrinology* 12: 83-105.
- 3C. 3-Ketosteroid receptors: Glucocorticoid receptor. IUPHAR database (IUPHAR-DB).
- 3C. 3-Ketosteroid receptors: Mineralocorticoid receptor. IUPHAR database (IUPHAR-DB).
- Haller J, Mikics E, Makara GB (2008) The effects of non-genomic glucocorticoid mechanisms on bodily functions and the central neural system. A critical evaluation of findings. *Front Neuroendocrinol* 29: 273-291.
- Karst H, Joëls M (1991) The induction of corticosteroid actions on membrane properties of hippocampal CA1 neurons requires protein synthesis. *Neurosci Lett* 130: 27-31.
- Karst H, Karten YJ, Reichardt HM, de Kloet ER, Schütz G, et al. (2000) Corticosteroid actions in hippocampus require DNA binding of glucocorticoid receptor homodimers. *Nat Neurosci* 3: 977-978.
- Qi AQ, Qiu J, Xiao L, Chen YZ (2005) Rapid activation of JNK and p38 by glucocorticoids in primary cultured hippocampal cells. *J Neurosci Res* 80: 510-517.
- Karst H, Berger S, Turiault M, Tronche F, Schütz G, et al. (2005) Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. *Proc Natl Acad Sci U S A* 102: 19204-19207.
- Prager EM, Brielmaier J, Bergstrom HC, McGuire J, Johnson LR (2010) Localization of mineralocorticoid receptors at mammalian synapses. *PLoS One* 5: e14344.
- Di S, Malcher-Lopes R, Halmos KC, Tasker JG (2003) Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. *J Neurosci* 23: 4850-4857.
- Di S, Malcher-Lopes R, Marcheselli VL, Bazan NG, Tasker JG (2005) Rapid glucocorticoid-mediated endocannabinoid release and opposing regulation of glutamate and gamma-aminobutyric acid inputs to hypothalamic magnocellular neurons. *Endocrinology* 146: 4292-4301.
- Johnson LR, Farb C, Morrison JH, McEwen BS, LeDoux JE (2005) Localization of glucocorticoid receptors at postsynaptic membranes in the lateral amygdala. *Neuroscience* 136: 289-299.
- Evanson NK, Tasker JG, Hill MN, Hillard CJ, Herman JP (2010) Fast feedback inhibition of the HPA axis by glucocorticoids is mediated by endocannabinoid signaling. *Endocrinology* 151: 4811-4819.