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Review

The interplay between rapid and slow corticosteroid actions in brain

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ABSTRACT

Stress causes the release of many transmitters and hormones, including corticosteroids. These molecules enter the brain and exert their effects through the mineralo- and glucocorticoid receptor. The former receptor plays an important role in neuronal stability. However, it also mediates rapid non-genomic corticosteroid effects that in synergy with other stress mediators activate limbic cells and promote behavioral choices allowing the organism to quickly respond to the imminent danger. Glucocorticoid receptors primarily mediate slow genomic effects, for instance in the hippocampus and prefrontal cortex, which are thought to contribute to contextual and higher cognitive aspects of behavioral performance several hours after stress. Rapid and slow effects interact and collectively contribute to successful behavioral adaptation. Long-term disturbances in the release pattern of corticosteroid hormones and in the responsiveness of their receptors give rise to structural and functional changes in neuronal properties which may contribute to the expression of psychopathology.

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1. Stress and the brain

"All you have to decide, is what to do with the time that is given you", says Gandalf to Frodo in Tolkien's The Lord of The Rings. This aphorism holds true for many individuals and may spring to mind especially when they are at the brink of a new era in their life, such as at the start or termination of career stages. But it is no less applicable to the molecules in our body, all of which have optimal time-domains in which they exert their actions. This chapter in the Festschrift for Willem Hendrik Gispen is about one such class of molecules, i.e. the adrenocortical steroids which are released after stress.

Stress refers to the subjective state of an individual when it experiences a situation that could (potentially) perturb homeostatis. When an organism is exposed to such a situation, it is able to adapt through the activation of two systems: the autonomic

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nervous system, which eventually causes the rapid release of (nor) adrenaline; and the hypothalamo-pituitary-adrenal axis, which results in the synthesis and secretion of corticosteroid hormones from the adrenal glands (De Kloet et al., 2005). The prevalent corticosteroid hormone in humans is cortisol while rodents generally produce corticosterone. The stress-induced surge of corticosteroid hormones is superimposed on ultradian pulses, which peak with hourly intervals (Lightman and Conway-Campbell, 2010). The amplitude of these ultradian pulses varies throughout the day, with high amplitudes around awakening and very low amplitudes at the end of the active period. The variation in peak amplitude gives rise to an overall circadian pattern of corticosteroid release. Stress-induced corticosteroid release is higher during the rising than the falling limb of an ultradian pulse, so that the timing of a stressor relative to the ultradian background variations in circulating corticosteroid level contributes to the biological response.

Corticosteroid hormones are very lipophilic and easily enter the brain. As true hormones they basically reach every cell in the brain but only affect those cells that express corticosteroid receptors. Based on the molecular structure and pharmacological profile two corticosteroid receptors were recognized in the eighties of the previous century (Reul and de Kloet, 1985; Evans and Arriza, 1989). First, the glucocorticoid receptor, which is quite ubiquitously expressed and binds cortisol or corticosterone with a Kd of 2–5 nM; this is a higher concentration than reached at the trough of the circadian rhythm, so that this receptor is only partly occupied under rest at the circadian trough but becomes substantially occupied after stress. Corticosteroid hormones bind with a 10-fold higher affinity to a second receptor type, the mineralocorticoid receptor. In the brain, expression levels of mineralocorticoid receptors are high in all hippocampal neurons, as well as neurons in the lateral septum and a restricted number of other brain nuclei. In epithelial cells, such as in the kidney, cortisol and corticosterone are converted by the 11-β-hydroxysteroid dehydrogenase isoform 2 into 11-keto-metabolites with very low affinity for the mineralocorticoid receptor, so that this receptor becomes available for binding by the less prevalent hormone aldosterone (Wyrwoll et al., 2011); aldosterone has hence always been considered as 'the' mineralocorticoid hormone. However, in non-epithelial cells, including most cells in the adult brain, 11-β-hydroxysteroid dehydrogenase isoform 2 is hardly expressed, so that corticosterone and cortisol are the main ligands of the mineralocorticoid receptor. This is particularly relevant for neurons that highly express both mineralo- and glucocorticoid receptors, such as pyramidal neurons in the CA1 hippocampal area and granule cells of the dentate gyrus. In these cells, the difference in affinity of the two receptor types results in a situation where low levels of corticosteroid hormones already cause substantial activation of mineralocorticoid receptors but only partial activation of glucocorticoid receptors (De Kloet et al., 2005). Glucocorticoid receptors become extensively activated with peak levels of the hormones, e.g. after stress or during high-amplitude ultradian pulses.

Until recently, the two receptor types were thought to reside in the cytoplasm when inactive, i.e. unbound to corticosteroids, in a complex with various chaperone molecules (Biddie and Hager, 2009). Upon binding of the steroids, the chaperones dissociate and the activated receptors translocate to the nucleus. There, they either homodimerize, binding to recognition sites (glucocorticoid response elements) in the DNA, or interact as monomers with other transcription factors. In both conformations, corticosteroid receptors long-lastingly change the expression of responsive genes, changing cell function with a delay of more than one hour (see Fig. 1).

Over the past decade, though, evidence has accumulated that corticosteroids, like other steroid hormones, can also alter neuronal function within minutes, via non-genomic pathways (Di et al., 2005; Groeneweg et al., 2011; Joëls et al., 2012). This probably involves corticosteroid receptors that reside in the plasma membrane rather than the nucleus. The pharmacological profile of these receptors mediating fast effects is highly comparable to that of the nuclear corticosteroid receptors, with two exceptions. First, the affinity for the membrane-located mineralocorticoid receptor appears to be 10-fold lower than for the nuclear variant (Karst et al., 2005), lending the former a potential role in the response to stress. Secondly, most studies agree that rapid non-genomic actions via glucocorticoid receptors are not blocked by the anti-glucocorticoid mifepristone, although successful blockade was observed in at least one study (see review Di et al., 2005; Joëls et al., 2012). Despite these discrepancies, there is so far little evidence for rapid effects being mediated by receptor molecules other than the well-known 'classical' corticosteroid receptors.

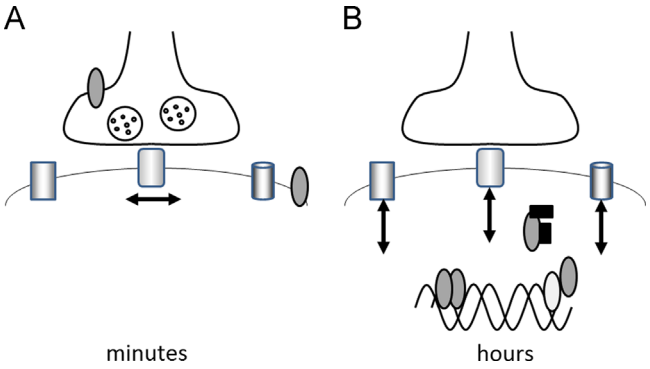

Fig. 1. Two modes of action by corticosteroid hormones. Corticosterone can change neuronal function over the course of minutes (left) to hours (right). In the rapid mode, the hormone binds to receptors (dark gray ovals) which are thought to reside in or close to the pre- and postsynaptic plasma membrane. This quickly-through pre- and postsynaptic pathways- alters the function of voltage-gated (gray rectangle) and ligand-gated ion channels (gray rounded rectangle). In the slow mode, corticosterone binds to intracellular receptors which in the unbound form are associated with chaperone molecules (black rectangles). Upon binding of corticosterone, these chaperones dissociate and the receptor-ligand complex moves to the nuclear compartment where the receptors either homodimerize and bind to specific promotor sites or interact as monomers with other transcription factors (light gray oval). As a consequence an approximate 2% of the genes are differently expressed, which may affect the function of ligand- and voltage-dependent ion channels as well as metabotropic receptors (gray cilinder). Cellular imaging studies have supplied evidence that in the rapid mode corticosteroid hormones promote lateral mobility of glutamate receptor subunits. Indirect evidence supports that in the slow mode the hormone rather promotes trafficking of ion channels and receptors between the intracellular compartment and the cell surface.

Apart from these two time-domains, i.e. minutes versus hours, a few studies have provided evidence for a third, intermediate domain of action. Thus, glucocorticoid receptors may interact with other molecules to accomplish biochemical and behavioral responses that appear with a delay of approximately 20 min (e.g. Gutierrez-Mecinas et al., 2011; Pfaff et al., 1971; Roozendaal et al., 2010). At this moment, very little is known about the underlying mechanism of this intermediate domain, but it has been suggested that it involves epigenetic pathways. All in all, variations in corticosteroid level can change the function of many neurons, over a wide range of time, starting directly after stress and lasting for hours to even days (for details see Joëls et al., 2012).

Obviously, corticosteroids do not work in splendid isolation, but interact with other neurotransmitters or hormones released in response to stress. While each of these molecules has its own target cells and mode of action, the fact that they may be present at the same time and same location after stress sets the stage for interactions, e.g. synergistic or additive effects. Such effects have indeed been observed. This 'neuro-symphony' of stress hormones collectively determines how an organism adapts to the changing environment (Joels and Baram, 2009). A full description of all