Molecular and Cellular Endocrinology 248 (2006) 9–14

www.elsevier.com/locate/mce

The role of 11β-hydroxysteroid dehydrogenases in the brain

Megan C. Holmes *, Jonathan R. Seckl

Endocrine Unit, Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom

Abstract

Glucocorticoids have a plethora of effects within the body to maintain homeostasis. In the brain they modify learning, memory and fear behaviours as well as regulating their own secretion by a negative feedback action. 11β-Hydroxysteroid dehydrogenases (11β-HSDs) are glucocorticoid metabolising enzymes that modify actions of glucocorticoids in a tissue specific manner. 11β-HSD1 regenerates active glucocorticoids from their inactive 11-keto derivatives, hence boosting tissue levels of corticosterone and cortisol. Removal of this enzyme (11β-HSD1$^{-/-}$ mice) results in apparent lower intra-hippocampal corticosterone levels and reduces glucocorticoid-associated cognitive decline during ageing. This low corticosterone tissue environment is maintained even though there is a hyperactive hypothalamic-pituitary-adrenal axis and elevated basal and stress-induced plasma corticosterone levels. Conversely, the major central effects of 11β-HSD2 are seen in development, as expression of 11β-HSD2 is high in fetal and certain parts of the neonate brain, but is confined to a few discrete regions of the adult brain. 11β-HSD2 acts as a dehydrogenase, inactivating corticosterone or cortisol through conversion to 11-dehydrocorticosterone and cortisone. Loss of 11β-HSD2 from the fetus and fetally derived tissues results in altered development of the cerebellum in the neonatal period and a life-long phenotype of anxiety, consistent with early life glucocorticoid programming.

Keywords: 11β-Hydroxysteroid dehydrogenase; Glucocorticoids; Hypothalamo-pituitary-adrenal axis; Cognition; Ageing; Anxiety

Glucocorticoid hormones play a major role in maintaining homeostasis, thereby influencing many systems of the body including the brain. Most neural pathways are modified by glucocorticoids, as target genes include neurotransmitter synthesis enzymes, receptors as well as enzymes involved in calcium activation and ion channels (e.g. K+ channels). High levels of glucocorticoids are deleterious to the homeostasis of the body, causing abnormalities in development through to potentiation of cognitive deficiencies seen in aging. Normally glucocorticoid levels are strictly controlled by a negative feedback action of glucocorticoids on the hypothalamo-pituitary-adrenal (HPA) axis; impairments in this regulation modify lifetime levels of glucocorticoids generating maladaptive effects in the brain.

1. 11β-Hydroxysteroid dehydrogenases

11β-Hydroxysteroid dehydrogenases (11β-HSDs) are enzymes that metabolise glucocorticoids and hence regulate the intracellular levels of steroids available to activate corticosteroid receptors. There are two isozymes, 11β-HSD type 1 and type 2, which in most tissues and conditions drive the enzyme reaction in opposite directions (Fig. 1). 11β-HSD2 inactivates glucocorticoids (corticosterone in the rat or mouse, cortisol in humans) to produce 11-dehydrocorticosterone (11-DHC), or cortisone, respectively. 11β-HSD2 acts solely as a dehydrogenase (unidirectional) with physiological corticosteroids, uses NAD^+ as a co-factor, has a low K_m for corticosterone and is highly expressed in classical aldosterone-selective target tissues (distal nephron, colon, sweat glands) (Brown et al., 1996a, 1996b). 11β-HSD1, however, is bidirectional in vitro but generally acts as a reductase, regenerating corticosterone and cortisol from their inactive 11-keto forms in vivo or in intact cells. 11β-HSD1 uses NADPH as co-factor, and acts as a lower affinity, high capacity enzyme with a general distribution of many metabolically active tissues in the body, notably in liver, adipose tissue, bone, the gonads (in some species) and the brain (Moisan et al., 1990; Seckl, 2004). 11β-HSD1 is the sole 11β-reductase in the rodent as infusion of 11-DHC in adrenalectomised 11β-HSD1-null mice did not produce any glucocorticoid activity, nor did they have detectable circulating corticosterone (Kotelevtsev et al., 1997).

* Corresponding author at: Endocrine Unit, Rm 3.10, Centre for Cardiovascular Science, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom. Tel.: +44 131 242 6736/7.
E-mail address: Megan.Holmes@ed.ac.uk (M.C. Holmes).

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doi:10.1016/j.mce.2005.12.002

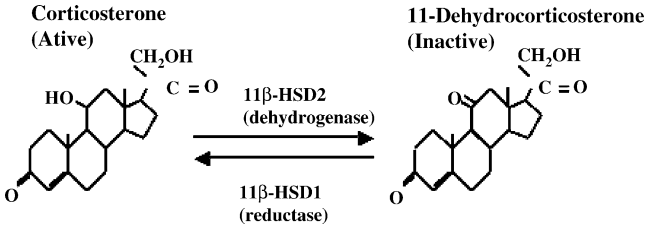

Fig. 1. Interconversion of corticosterone to 11-dehydrocorticosterone by 11β-hydroxysteroid dehydrogenases (11β-HSDs), active glucocorticoids (corticosterone) are metabolised by 11β-HSD2 to their inactive 11-keto derivative (11-dehydrocorticosterone) while regeneration to active steroid occurs with 11β-HSD1 which acts as a reductase.

2. 11β-HSD1 and HPA axis regulation

Glucocorticoid secretion is regulated by the neuroendocrine axis, the HPA axis, which is activated in stress and terminated by glucocorticoids themselves in a negative feedback loop. Significantly, areas of 11β-HSD1 expression include central sites of negative feedback of glucocorticoids, including the paraventricular nucleus of the hypothalamus, the hippocampus and the cerebral cortex. Furthermore, the extensive expression of 11β-HSD1 in the liver may potentially provide a significant source of circulating corticosterone, which will have a major effect on the kinetics of production and removal of the active hormone.

To determine the role of 11β-HSD1 in HPA axis regulation, we studied mice lacking 11β-HSD1 activity. 11β-HSD1$^{-/-}$ mice (on a 129/MF1 strain background) have hypertrophied adrenals and elevated basal ACTH and corticosterone levels at the nadir of the rhythm (Harris et al., 2001; Kotelevtsev et al., 1997). The increased ACTH level is apparently sufficient to underpin the adrenal hypertrophy. Moreover, in vitro, 11β-HSD1$^{-/-}$ adrenal glands are hyperesponsive to ACTH. These effects are compatible with the decreased half-life of active glucocorticoids in this mutant due to lack of regeneration in the liver and other sites. Furthermore, CRF mRNA levels in the paraventricular nucleus (PVN) of the hypothalamus are unaltered (Harris et al., 2001), suggesting the net effect (of increased corticosterone, decreased half-life and decreased regeneration occurring centrally) of 11β-HSD1$^{-/-}$ is to maintain normal central drive. Other factors which regulate glucocorticoid action such as corticosteroid binding globulin (CBG) and glucocorticoid receptors (GR) are also not affected by loss of 11β-HSD1 activity (Harris et al., 2001).

3. Stress

When the HPA axis is activated by restraint stress, the peak corticosterone response is exaggerated in 11β-HSD1-null mice but peak ACTH levels are unaltered. These data suggest that the corticosterone hypersecretion is mainly due to the hypersensitive adrenal. However, the turn-off phase of the ACTH response, which correlates with glucocorticoid negative-feedback efficiency, is delayed. Administration of cortisol, the human glucocorticoid, 2 h prior to restraint stress, causes a greater inhibition of the subsequent corticosterone response to restraint stress in wild-type mice than 11β-HSD1$^{-/-}$ mice, providing further evidence for attenuated negative feedback in 11β-HSD1-null mice. It therefore appears that although there are elevated levels of corticosterone circulating, there is an impaired glucocorticoid signal at feedback sites, due to the loss of 11β-HSD1 activity (Harris et al., 2001). This is consistent with the finding that the brain accumulates significantly less ^{3}H-corticosterone after a 7-day infusion in knock out mice compared to wild-type, suggesting 11β-HSD1 activity is required for normal intracellular glucocorticoid levels in the brain (Yau et al., 2001).

Stress itself has been shown to regulate 11β-HSD1 expression in a time- and tissue-dependent manner. While shorter term stressors or glucocorticoid treatment of 2–10 days induces a rise in hippocampal 11β-HSD1 expression (Jamieson et al., 1997; Low et al., 1994), more chronic (1 month) psychosocial stress causes a decrease in expression (Jamieson et al., 1997; Seckl, 1997). This suggests the rise in 11β-HSD1 activity in response to the acute stress is a compensatory action to increase the negative feedback signal to switch-off the HPA axis, whereas the protective response against chronic stress is to decrease 11β-HSD1 and thus ameliorate glucocorticoid excess at the tissue level and hence minimise their adverse effects.

The circadian periodicity of plasma corticosterone is also modified in 11β-HSD1-null mice. The evening elevation in corticosterone is shifted much earlier, producing an extended period of hypersecretion (Harris et al., 2001). 11β-HSD1 activity is not thought to be regulated in a circadian pattern, as 11β-HSD1 mRNA expression is unaltered at 8 a.m. versus 8 p.m. (Harris et al., 2001). It therefore is possible that 11β-HSD1 may modify central glucocorticoid signalling on circadian pathways be explicit. The mechanisms and loci of these interesting effects remain to be determined.

4. Strain variability in HPA axis regulation

It is well documented that different strains of rats and mice exhibit different degrees of HPA axis activity, both basally and in response to stress. Notably, the BalbC mouse strain has large adrenals and an exaggerated stress responsivity compared to the C57BL/6 mouse and this results in altered behaviour of increased aggressiveness and anxiety (Zaharia et al., 1996). In fact the C57BL/6 strain shows a particularly tight control of glucocorticoid secretion in most circumstances. It therefore becomes very interesting to determine how different strains respond to loss of 11β-HSD1, as this may reflect light upon the observed variation within a human population. The 11β-HSD1 deletion was initially made on a 129 background strain and then crossed on to a robust outbred strain, MF1. The results on HPA accommodation to 11β-HSD1 deletion in these strains are given in the section above. However, when the gene deletion was backcrossed onto a C57BL/6J background (>10 generations), the HPA phenotype is modified slightly. C57BL/6J 11β-HSD1$^{-/-}$ mice have hypertrophied adrenals and elevated glucocorticoid responses to stress as reported on other backgrounds, however basal corticosterone and ACTH levels remain unchanged from C57BL/6 controls. This appears to be due to an elevation in levels