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Molecular and Cellular Endocrinology 248 (2006) 15–23

MCE
Molecular and Cellular Endocrinology

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Why is 11β-hydroxysteroid dehydrogenase type 1 facing the endoplasmic reticulum lumen? Physiological relevance of the membrane topology of 11β-HSD1

Alex Odermatt [a,*], Atanas G. Atanasov [a], Zoltan Balazs [a], Roberto A.S. Schweizer [a], Lyubomir G. Nashev [a], Daniela Schuster [b], Thierry Langer [b]

[a] *Department of Nephrology and Hypertension, Department of Clinical Research, University of Berne, Freiburgstrasse 15, 3010 Berne, Switzerland*

[b] *Institute of Pharmacy, University of Innsbruck, Innrain 52, A-6020 Innsbruck, Austria*

Abstract

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is essential for the local activation of glucocorticoid receptors (GR). Unlike unliganded cytoplasmic GR, 11β-HSD1 is an endoplasmic reticulum (ER)-membrane protein with lumenal orientation. Cortisone might gain direct access to 11β-HSD1 by free diffusion across membranes, indirectly via intracellular binding proteins or, alternatively, by insertion into membranes. Membranous cortisol, formed by 11β-HSD1 at the ER-lumenal side, might then activate cytoplasmic GR or bind to ER-lumenal secretory proteins. Compartmentalization of 11β-HSD1 is important for its regulation by hexose-6-phosphate dehydrogenase (H6PDH), which regenerates cofactor NADPH in the ER lumen and stimulates oxoreductase activity. ER-lumenal orientation of 11β-HSD1 is also essential for the metabolism of the alternative substrate 7-ketocholesterol (7KC), a major cholesterol oxidation product found in atherosclerotic plaques and taken up from processed cholesterol-rich food. An 11β-HSD1 mutant adopting cytoplasmic orientation efficiently catalyzed the oxoreduction of cortisone but not 7KC, indicating access to cortisone from both sides of the ER-membrane but to 7KC only from the lumenal side. These aspects may be relevant for understanding the physiological role of 11β-HSD1 and for developing therapeutic interventions to control glucocorticoid reactivation.

Keywords: Glucocorticoid receptor; 11β-Hydroxysteroid dehydrogenase; Cortisone; 7-Ketocholesterol; Hexose-6-phosphate dehydrogenase; Membrane topology

1. Introduction

Glucocorticoids (cortisol and corticosterone) and mineralocorticoids (aldosterone) are produced in the adrenal cortex (Lin and Achermann, 2004; Stratakis and Bossis, 2004). Most of their effects are mediated through activation of steroid binding receptors, e.g. glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). Both receptors are located in the cytoplasm in their unliganded form (Funder, 1996) and undergo a conformational activation, followed by dimerization and translocation into the nucleus upon hormone binding (Fig. 1). Cortisol is one of the strongest known endogenous suppressors of the immune system and plays an essential modulatory role during inflammation and infection (Rook, 1999). Its secretion is enhanced by stress-related physiological factors including hypoglycemia, fever and pain (Miller and O'Callaghan, 2002). In addition, cortisol regulates bone metabolism as well as carbohydrate and amino acid metabolism, which is related with the origin of its name 'gluco'-corticoid, derived from its relevance for glucose homeostasis (Gerich, 1993). Aldosterone, the principle mineralocorticoid hormone, is controlled by angiotensin II of the rennin–angiotensin system and exerts an essential role in sodium re-absorption in the kidney and blood pressure control (Agarwal and Mirshahi, 1999; Bonvalet, 1998).

The multiple effects mediated by GR and MR require a tight regulation allowing time-dependent and tissue-specific modulation of the transcriptional regulation of their target genes. Disturbed GR and MR action has been associated with several disease states including inflammation, osteoporosis, cataract formation, obesity, diabetes type 2, hypertension and cardiovascular disease (Carnahan and Goldstein, 2000; Cooper, 2004; De Mello, 2004; Freel and Connell, 2004; Rosmond, 2005). The importance of GR and MR during development is further indicated by the fact that MR- and GR-knock-out mice suffer

* Corresponding author. Tel.: +41 31 632 9438; fax: +41 31 632 9444.
E-mail address: alex.odermatt@dkf.unibe.ch (A. Odermatt).

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doi:10.1016/j.mce.2005.11.040

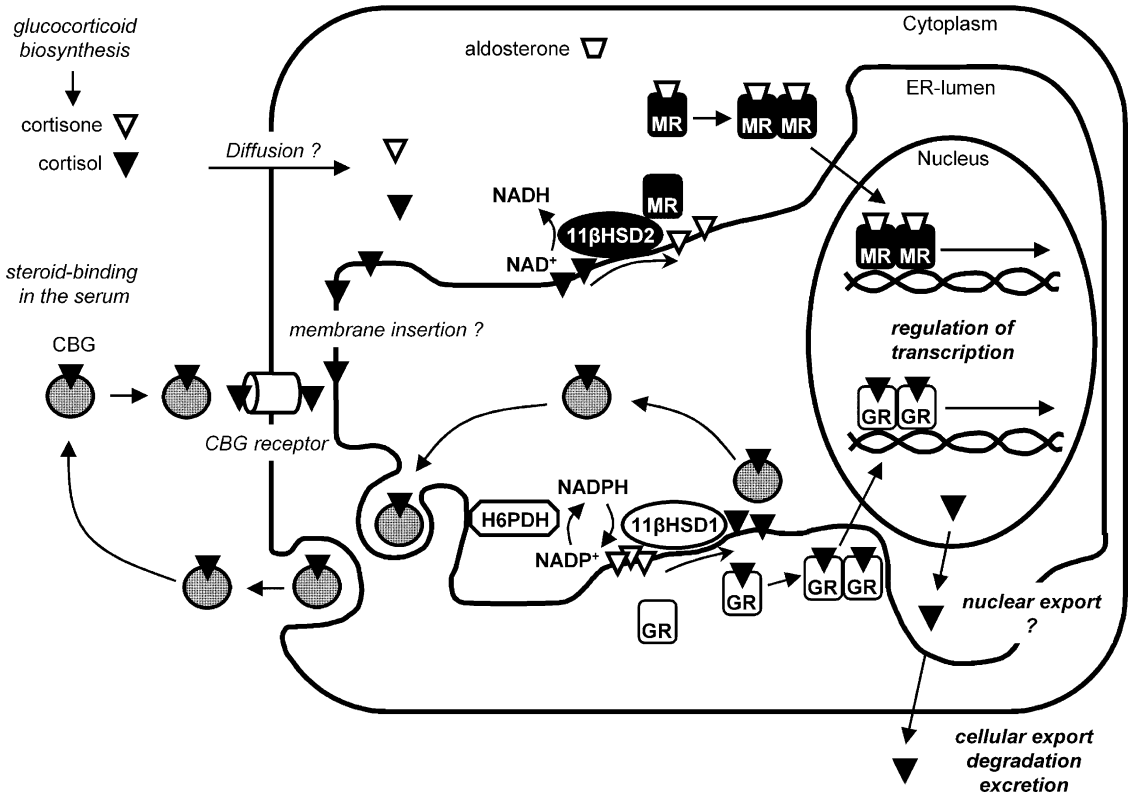

Fig. 1. Schematic representation of glucocorticoid action.

from severe complications and die within a few days after birth (Wintermantel et al., 2004).

Diseases due to disturbed glucocorticoid action may be caused by defects at various steps of the regulatory pathway including alterations in the (A) biosynthesis in the adrenal glands, (B) levels of serum binding proteins such as cortisol binding globulin-α (CBG) or albumin, (C) uptake into the target cell, (D) intracellular binding or metabolism, (E) receptor availability and functionality, (F) assembly of the transcriptional complex and (G) export of the steroid hormone, metabolism and excretion from the body (Fig. 1).

In the past 2 decades it became evident that the intracellular availability of active glucocorticoids to the cognate receptor is enzymatically regulated by 11β-hydroxysteroid dehydrogenases (11β-HSDs) and disturbed 11β-HSD function has been associated with several of the above mentioned disease states (Frey et al., 2004; Odermatt, 2004; Tomlinson et al., 2004; White et al., 1997).

2. The pre-receptor regulation of glucocorticoid action by 11β-HSDs

The endogenous 11-ketoglucocorticoids cortisone (humans) and 11-dehydrocorticosterone (rodents) are inactive and require conversion to their active 11β-hydroxy derivatives cortisol and corticosterone. 11β-HSD1, the enzyme catalyzing this conversion, belongs to the short-chain reductase/dehydrogenase family and plays an essential role in the local activation of GR. Recent investigations from transgenic mice and from humans revealed an association between enhanced glucocorticoid reactivation through elevated 11β-HSD1 expression in adipose tissue and the development of visceral obesity and diabetes type 2, suggesting that this enzyme represents a promising target for therapeutic intervention (reviewed in Odermatt, 2005; Tomlinson et al., 2004). A second enzyme of this family, 11β-HSD2, catalyzes the reverse reaction and protects MR from activation by glucocorticoids, thereby rendering specificity of this receptor for the mineralocorticoid aldosterone (White et al., 1997). Impaired 11β-HSD2 activity is most critical in MR target tissues, where it leads to elevated levels of 11β-hydroxyglucocorticoids and causes glucocorticoid-induced MR activation with sodium retention and hypertension. Thus, the control of the ratio of active to inactive glucocorticoid hormones is important for appropriate GR and MR action.

3. Molecular determinants of the membrane topology of 11β-HSDs

Both 11β-HSD1 and 11β-HSD2 contain an N-terminal membrane anchor that is sufficient for localization in the endoplasmic reticulum (ER) membrane (Odermatt et al., 1999). While 11β-HSD1 has a single transmembrane helix determining its ER-lumenal orientation (Mziaut et al., 1999; Odermatt et al., 1999), 11β-HSD2 has three membrane spans and its catalytic moiety is facing the cytoplasm (Fig. 2) (Naray-Fejes-Toth and Fejes-Toth, 1996, 1998; Odermatt et al., 1999). Exchange of the membrane anchoring region was sufficient for reorientation of the corresponding enzyme in the ER-membrane. All three membrane