

Publication

11beta-Hydroxysteroid dehydrogenase 1 reductase activity is dependent on a high ratio of NADPH/NADP(+) and is stimulated by extracellular glucose

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To assess the impact of the NADPH/NADP(+) ratio and the influence of extracellular glucose on 11beta-hydroxysteroid dehydrogenase 1 (11beta-HSD1) activity, we applied microsomal preparations and intact HEK-293 cells expressing 11beta-HSD1 in the presence or absence of hexose-6-phosphate dehydrogenase (H6PDH). A NADPH/NADP(+) ratio of ten or higher was required for efficient microsomal 11beta-HSD1 reductase activity. Measurements in intact cells suggested that the ER-luminal NADPH concentration is highly sensitive to fluctuating extracellular glucose levels. Lowering glucose in the culture medium dose-dependently decreased 11beta-HSD1 reductase activity and diminished the cortisol/cortisone ratio measured after 24h of incubation. Coexpression with H6PDH potentiated 11beta-HSD1 reductase activity at high glucose. This effect was significantly decreased at low glucose, with concomitantly increased 11beta-HSD1 dehydrogenase activity. In contrast, 11beta-HSD1 reductase activity in H4IIE liver cells and in 3T3-L1 adipocytes was less sensitive to changes in the medium. 11beta-HSD1 dehydrogenase activity was observed in H4IIE cells only at subphysiological glucose levels, indicating a highly efficient supply of substrate for H6PDH and NADPH generation in the ER-lumen. Our results suggest significant cell type-specific differences in ER-luminal NADPH generation that might allow a fine-tuned regulation of glucocorticoid action.

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