

FIGURE 406-5 ACTH effects on adrenal steroidogenesis. ACTH, adrenocorticotropic hormone; binding protein; MRAP, MC2R-accessory protein; protein kinase A catalytic subunit (C; *PRKACA*), PKA regulatory subunit (R; *PRKAR1A*); StAR, steroidogenic acute regulatory (protein); TSPO, translocator protein.

Following its release from the adrenal, cortisol circulates in the bloodstream mainly bound to cortisol-binding globulin (CBG) and to a lesser extent to albumin, with only a minor fraction circulating as free, unbound hormone. Free cortisol is thought to enter cells directly, not requiring active transport. In addition, in a multitude of peripheral target tissues of glucocorticoid action, including adipose, liver, muscle, and brain, cortisol is generated from inactive cortisone within the cell by the enzyme 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) (Fig. 406-6). Thereby, 11 β -HSD1 functions as a tissue-specific prereceptor regulator of glucocorticoid action. For the conversion

of inactive cortisone to active cortisol, 11 β -HSD1 requires nicotinamide adenine dinucleotide phosphate (NADPH [reduced form]), which is provided by the enzyme hexose-6-phosphate dehydrogenase (H6PDH). Like the catalytic domain of 11 β -HSD1, H6PDH is located in the lumen of the endoplasmic reticulum, and converts glucose-6-phosphate (G6P) to 6-phosphogluconate (6PGL), thereby regenerating NADP⁺ to NADPH, which drives the activation of cortisol from cortisone by 11 β -HSD1.

In the cytosol of target cells, cortisol binds and activates the glucocorticoid receptor (GR), which results in dissociation of heat shock

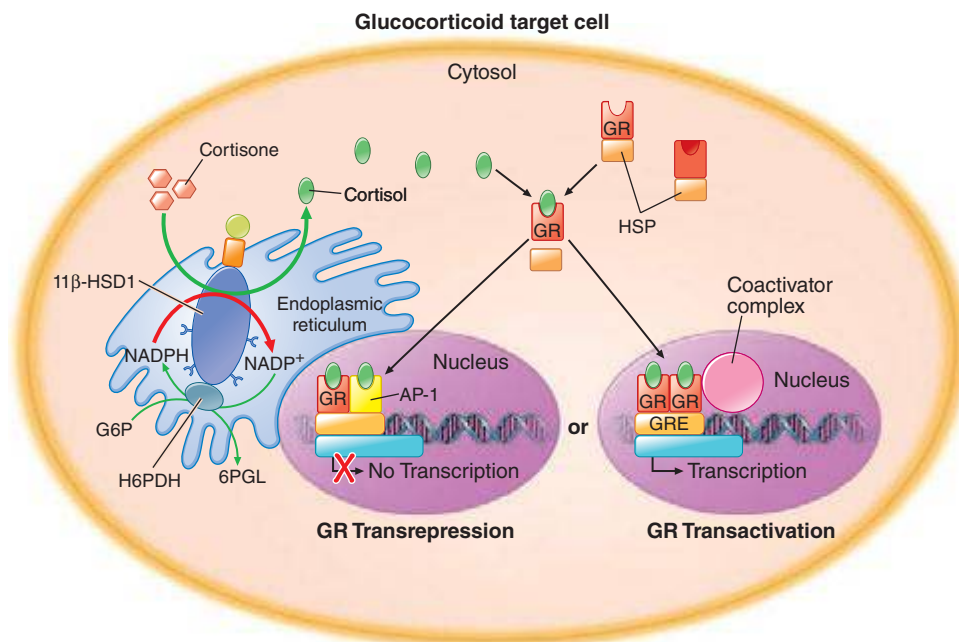


FIGURE 406-6 Prereceptor activation of cortisol and glucocorticoid receptor (GR) action. AP-1 activator protein-1; G6P, glucose-6-phosphate; GRE, glucocorticoid response elements; HSP, heat shock proteins; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); 6PGL, 6-phosphogluconate.