

receptor and subsequent dimerization ([Fig. 386-6](#)). Cortisol-bound GR dimers translocate to the nucleus and activate glucocorticoid response elements (GREs) in the DNA sequence, thereby enhancing transcription of glucocorticoid-regulated genes (GR transactivation). However, cortisol-bound GR can also form heterodimers with transcription factors such as AP-1 or NF- κ B, resulting in transrepression of proinflammatory genes, a mechanism of major importance for the anti-inflammatory action of glucocorticoids. It is important to note that corticosterone also exerts glucocorticoid activity, albeit much weaker than cortisol itself. However, in rodents, corticosterone is the major glucocorticoid, and in patients with 17-hydroxylase deficiency, lack of cortisol can be compensated for by higher concentrations of corticosterone that accumulates as a consequence of the enzymatic block.

Cortisol is inactivated to cortisone by the microsomal enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) ([Fig. 386-7](#)), mainly in the kidney, but also in the colon, salivary glands, and other target tissues. Cortisol and aldosterone bind the mineralocorticoid receptor (MR) with equal affinity; however, cortisol circulates in the bloodstream at about a 1000-fold higher concentration. Thus, only rapid inactivation of cortisol to cortisone by 11 β -HSD2 prevents MR activation by excess cortisol, thereby acting as a tissue-specific modulator of the MR pathway. In addition to cortisol and aldosterone, DOC ([Fig. 386-1](#)) also exerts mineralocorticoid activity. DOC accumulation due to 11 β -hydroxylase deficiency or due to tumor-related excess production can result in mineralocorticoid excess.