11β-Hydroxysteroid dehydrogenase type 1: potential therapeutic target for metabolic syndrome

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Abstract:
Overweight and associated metabolic syndrome is one of the greatest health threat to the modern society. Cortisol excess and the glucocorticoid receptor signaling pathway in the metabolically active tissues have been implicated in the development of diabetes and obesity. The key enzyme in the regeneration of intracellular cortisol is 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). 11β-HSD1 increases local cortisol production in metabolically active tissue types such as adipose and liver. Recent studies have shown that mice deficient in this enzyme are resistant to diet induced obesity and have increased insulin and leptin sensitivity. Clinical and preclinical studies indicate that 11β-HSD1 inhibitors are likely to exert major pharmacological actions in metabolically active tissues. These effects suggest that inhibition of 11β-HSD1 in vivo may be a novel therapeutic target for obesity, diabetes, and metabolic syndrome. The advancement of numerous structural classes of selective 11β-HSD1 inhibitors further indicates that more refined design and screening for isoform and tissue selectivity would yield potential therapeutics in this area.

Key words:
11β-hydroxysteroid dehydrogenase type 1, metabolic syndrome, obesity, diabetes, glucocorticoids, liver, adipose