11ß-hydroxysteroid dehydrogenase type 1 as a cause of and target for metabolic syndrome and age-related cognitive impairment: hope or hype?

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In Cushing's syndrome, chronic glucocorticoid excess exerts a host of adverse effects on body (visceral obesity, insulin resistance/type 2 diabetes, dyslipidaemia, atherosclerosis) and brain (depression, cognitive impairment). However, in most cases of these prevalent disorders plasma cortisol levels are not elevated and thus any relevance of glucocorticoids to pathogenesis has been obscure. Glucocorticoid action on target tissues is determined by the density of nuclear corticosteroid receptors and by intracellular metabolism by 11ß-hydroxysteroid dehydrogenases (11β-HSDs) which catalyse the interconversion of active cortisol (corticosterone in rodents) and inert cortisone (11-dehydrocorticosterone). In metabolic tissues (liver, adipose) and CNS the 11ß-HSD type 1 isozyme predominates which catalyses the regeneration of active steroids, thus amplifying glucocorticoid action.

Obese humans and rodents show ~2-fold increased 11ß-HSD1 selectively in adipose tissue. Transgenic modelling of this recapitulates metabolic syndrome whereas 11ß-HSD1 knock-out (11β-HSD1$^{-/-}$) mice have improved glucose tolerance, a 'cardioprotective' lipid profile, insulin sensitization, reduced visceral fat accumulation with high fat diet and lower weight gain despite hyperphagia. 11β-HSD1$^{-/-}$ mice also have increased angiogenesis in response to experimental myocardial infarction and resist atherosclerosis. In obese diabetic humans, selective 11ß-HSD1 inhibitors have shown beneficial effects in early phase clinical trials.

11ß-HSD1 is also highly expressed in the adult CNS and its inhibition protects hippocampal cells from neurotoxic challenge in vitro. 11ß-HSD1 is elevated in aged rat hippocampus and correlates with the degree of cognitive decline suggesting an aetiological role. Importantly, 11ß-HSD1$^{-/-}$ mice resist glucocorticoid-associated impairments of cognitive function with ageing and indeed the 11ß-HSD inhibitor carbenoxolone improves cognitive performance in elderly humans. Thus 11β-HSD1 appears a promising target for therapy of metabolic syndrome/obesity spectrum disorders and age-related cognitive impairment and is a prototype for tissue-specific manipulation of the effects of glucocorticoids.