Abstract

11β-hydroxysteroid dehydrogenase (11HSD1) is an oxidoreductase which catalyzes conversion of inactive 11-oxo steroid derivatives into active 11-hydroxy forms. 11HSD1 elevates intracellular level of active glucocorticoid (GC) hormones: cortisol in human tissues and corticosterone in rodents, therefore local level of active GCs can be set independently from systemic secretion driven by hypothalamo-pituitary-adrenal axis (HPA axis). Chronic systemic excess of GCs results in development of Cushing´s syndrome which is characterised by central obesity and other metabolic disturbances. Despite normal serum levels of GCs, the patients with idiopathic obesity also develop metabolic syndrome. It was suggested that GCs could be elevated locally in target tissues due to enhanced 11HSD1 activity. This hypothesis was confirmed in transgenic rodent models.

Prague hereditary hypertriglyceridemic (HHTg) rats represent a non-obese model of metabolic syndrome without genetic manipulations or specific mutations. The strain was bred by cross-mating of Wistar rat individuals with elevated serum levels of triglycerides (TGs). The strain exhibit hypertriglyceridemia and hypertension. When kept on high carbohydrate diet HHTg rats exhibit alterations in glucose homeostasis. Since there are no data that would describe relationship between GCs and metabolic syndrome in HHTg rats we decided to study local metabolism of GCs in HHTg rats under basal and stress conditions. We also tested effects of chronic treatment of carbenoxolone (CBX), a nonselective inhibitor of hydroxysteroid dehydrogenases, and effect of chronic treatment of Compound 544 (C544), a selective inhibitor of 11HSD1 on different components of GC action and on selected serum parameters in HHTg rats.

We used enzymatic assays to study the level of active 11HSD1 protein (activity) and molecular biology techniques to determine 11HSD1 expression in the liver, subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and skeletal muscle of female HHTg rats. The same approach was used to study mRNA expression of hexoso-6-phosphate dehydrogenase (H6PDH), an enzyme that cooperates with 11HSD1, and glucocorticoid receptor (GR).

We found elevated 11HSD1 in HHTg rats compared to Wistar rats in all tested tissues. Despite the fact that 11HSD1 activity did not always correlated with mRNA expression it seems that HHTg rats might suffer from increased intracellular level of GCs. Fasting induced similar tissue-specific changes in 11HSD1 activity and expression in both Wistar and HHTg rats. In liver, 11HSD1 was downregulated while in adipose tissue it was upregulated. No fasting-mediated changes were observed in skeletal muscle. Similar changes were found in H6PDH expression. 11HSD1 activity and expression was downregulated upon CBX treatment in the liver of HHTg rats, however this was not followed by improvement of metabolic syndrome symptoms. No changes were found in adipose tissue and skeletal muscle. In contrast to CBX treatment, C544 treatment lowered hypertriglyceridemia and elevated serum HDL lipoprotein fraction in HHTg rats. It also decreased systemic levels of corticosterone (CS), a main GC in rodents.

In conclusion, HHTg rats exhibit altered intracellular GC metabolism compared to Wistar rats. Fasting induced tissue-specific changes in local GC metabolism. These changes were similar in both strains. Nonselective 11HSD1 inhibition did not ameliorate metabolic syndrome in HHTg rats in contrast to selective 11HSD1 inhibition that resulted in lowered serum TGs. It seems that 11HSD1 is a promising therapeutic target and should be considered for further research of metabolic syndrome.