

Abstract

The pathogenesis of insulin resistance is a complex and still intensively studied issue. Endocrine and paracrine activity of the adipose tissue together with mitochondrial dysfunction are the most discussed potential factors included in the development of insulin resistance.

In the first part of our study we examined the involvement of the adipose tissue and its secretory products in the etiopathogenesis of insulin resistance in patients with Cushing's syndrome, acromegaly and simple obesity. We focused on three important regulators of metabolic homeostasis — fibroblast growth factors 21 and 19 (FGF-21 and FGF-19) and adipocyte fatty acid binding protein (FABP-4).

We found significantly elevated circulating levels of FGF-21 and FABP-4 accompanying insulin resistance in both patients with simple obesity and patients with obesity connected to Cushing's syndrome, as compared to healthy controls. The concentrations of both substances were comparable between hypercortisolic and obese patients. This finding together with the absence of correlation between the levels of FGF-21 resp. FABP-4 and cortisol suggest that the reason for elevation of their concentrations is obesity and its metabolic consequences themselves rather than the effect of hypercortisolism on FGF-21 and FABP-4 production. We found no significant changes in concentrations of FGF-19 in the studied groups of patients. The absence of significant differences in the levels of FGF-21, FGF-19 and FABP-4 between acromegalic patients and healthy controls suggests that endocrine dysfunction of the adipose tissue is not crucial for the development of insulin resistance in acromegaly. The primary etiopathogenic factor of insulin resistance in patients with overproduction of growth hormone are the numerous postreceptor interactions between growth hormone and insulin signaling pathways.

The second aim of our study was to examine the role of mitochondrial dysfunction in the pathogenesis of insulin resistance. We studied the activities and concentrations of enzymes involved in mitochondrial glucose and lipid metabolism, respiratory chain, as well as their expressions in subcutaneous adipose tissue.

We found signs of mitochondrial dysfunction in all studied groups of patients, i.e. patients with Cushing's syndrome, acromegaly as well as simple obesity, as compared with healthy controls. The extent of this dysfunction corresponded approximately with the percentage of subjects with glucose metabolism disturbances present in particular groups. The changes were mostly expressed in patients with simple obesity, on the other hand, the mildest changes were found in hypercortisolic patients. Our results suggest that neither the overproduction of cortisol nor growth hormone are the etiopathogenic reasons for detected mitochondrial dysfunction. We assume that the findings of mitochondrial dysfunction in patients with overproduction of cortisol resp. growth hormone/IGF-1 are only indirect consequences of prolonged metabolic effects of pathologically elevated hormone levels resp. negative interactions of growth hormone with insulin signaling pathways.

Keywords: obesity, insulin resistance, cortisol, growth hormone, fibroblast growth factors 21 and 19, adipocyte fatty acid binding protein, mitochondrial dysfunction.