# Role of Mitochondrial Translocator Protein (TSPO) in oxidative damage in heart and skeletal muscle

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Obesity, mainly its abdominal form, is considered a relevant risk factor not only in type 2 diabetes, lipid disorders and hypertension but also in the development of coronary artery disease. During the past decade, evidence has been collected showing that patients, especially elderly, with several chronic diseases and elevated BMI may demonstrate lower all-cause and cardiovascular mortality compared with patients of normal weight. For example, among patients with type 2 diabetes and cardiovascular comorbidity, overweight and obese patients had a lower mortality compared with normal-weight subjects. These paradoxical findings are known as the 'obesity paradox'. In our experimental model, diabetic rats fed with a normocaloric diet, showed a significant loss of muscle tissue compared to the corresponding controls (rats fed with a normocaloric diet). On the other hand, hyperlipidemic diabetic rats as well as rat fed with an hyperlipidemic diet, didn't show any significative difference in lean mass composition. In addition, the impairment of body mass observed in hyperglycemic rats was associated with a decreased cardiac function, less pronounced in hyperlipidemic diabetic rats. This effect was accompanied by a down-expression of mitochondrial Translocator Protein (TSPO) in hyperlipidemic diabetic rats as compared with controls. TSPO plays a central role in the regulation of mitochondrial function modulating the crosstalk between Inner Membrane Anion Channel (IMAC) and Permeability Transition Pore (PTP) in the mitochondrion. To date, the role of TSPO in preventing mitochondrial dysfunction and apoptosis is unclear. In response to oxidative stress and impairment of intracellular antioxidant systems, TSPO down-regulation might represent a defensive mechanism of cardiomyocyte aimed to prevent superoxide anion efflux from the mitochondrial matrix and the consequent opening of PTP. TSPO has also been associated with cholesterol import into mitochondria, a key step in steroidogenesis; as a consequence, its down-regulation can further reduce PTP opening induced by mitochondrial cholesterol accumulation and oxysterol overproduction. Despite of TSPO down-expression, in hyperglycemic/hyperlipidemic rats we observed an increase in plasmatic levels of 3 alpha, 5alpha-tetra-hydro-progesterone (allopregnanolone) suggesting an enhanced activity of cytoplasmic enzymes involved in biosynthesis of allopregnanolone able to protect heart and skeletal muscle tissues by oxidative damage. The discussion over the molecular mechanisms underlying the obesity paradox cannot lead to an underestimation of obesity as a crucial risk factor for the development of cardiovascular and metabolic diseases; however, the preservation of cardiac and muscle tissues from mitochondrial-induced oxidative damage observed in hyperglycemic/hyperlipidemic rats suggests the need of further investigations aimed to identify new therapeutic strategies in cardiovascular diseases.

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