HYPERCHOLESTEROLEMIA MODULATES MITOCHONDRIAL DYSFUNCTION IN RAT DIABETIC CARDIOMYOPATHY

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Metabolic syndrome (MS) represents a clustering of risk factors related to an elevated incidence of cardiovascular disease (CVD) and type 2 diabetes. Among them, hyperglycemia and hyperlipidemia represent two very important factors which determine the development of diabetes-induced cardiomyophaty. In particular, it has been demonstrated that oxidative stress and mitochondrial dysfunction are two key elements triggering cardiomyocyte injury and death. Despite this evidence, molecular mechanisms underlying the cardiomyocyte damage during the early stages of cardiac dysfunction need to be better clarified.

The purpose of our study is to investigate the impact of glucose and lipid metabolism on free radical overproduction and mitochondrial dysfunction.

In our experimental model, rats were fed with a normocaloric diet (NPD group) or with a high fat diet (HFD group), respectively. One month later, streptozocin (STZ, 35 mg/Kg, i.p.) was administered in a subgroup of both NPD and HFD rats to induce diabetes and the sacrifice was carried out after sixty days.

Our results revealed that hyperglicemia (NPD+STZ) or hyperlipidemia significantly increased the diameter of the left ventricular chamber in diastole (LVEDd) and in systole (LVESd). In addition, these pathological conditions reduced ejection fraction (EF) and fractional shortening (FS) compared to control (NPD). Surprisingly, cardiac dysfunction was less marked in diabetic hyperlipidemic (HFD+STZ) rats, suggesting an adaptative response to injury of diabetic heart in the presence of hyperlipidemia.

This event was accompanied by an overproduction of superoxide anion by NADPH oxidase which was more expressed in NPD+STZ rats as compared to HFD+STZ; on the other hand, MnSOD expression profile showed a better ability to scavenger free radicals in HPD+STZ hearts as compared to NPD+STZ. These data confirm that oxidative stress plays a very important role in myocardial damage induced by diabetes and that mitochondrion function is a key factor in maintaining cardiomyocyte calcium homeostasis and energy needed to ensure cardiac function. In our experimental conditions, we also observed that decreased levels of free radicals were 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, it might represent a defensive mechanism of cardiomyocyte aimed to prevent the 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. Therefore, TSPO down-regulation might represent a defensive mechanism of cardiomyocyte aimed to inhibit the opening of PTP and apoptosis. Our results confirm this hypothesis and show for the first time that in response to free radical overproduction, hypercholesterolemia is able to prevent PTP opening, through a down regulation of TSPO in HFD+STZ hearts as compared to NPD+STZ group. This event is also related to a prevention of apoptotic cell death, as shown by enhanced levels of Bcl-2.

Our researches show that modulation of cholesterol metabolism is a key event in the regulation of mitochondrial function under diabetes. However, further studies are needed to better clarify the mechanisms underlying the preservation of myocardium from mitochondrial-induced oxidative damage observed in HFD+STZ rats and to identify new therapeutic strategies in diabetic cardiomyophaty.