Hyperlipidemia-induced modulation of mitochondrial dysfunction in rat diabetic cardiomyopathy

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Diabetes is a metabolic, heterogeneous disorder characterized by a complex pathogenesis which can be related to genetic susceptibility, obesity, sedentary lifestyle and hypercaloric dietary supply. Hyperglycemia and hyperlipidemia are the main metabolic dysfunctions characterizing diabetic patients thereby representing the most important risk factors for cardiovascular diseases which are the leading cause of death among people with diabetes. Despite this evidence, to date, the exact role of hyperglycemia and hyperlipidemia in the onset of cardiovascular diseases and, in particular, in diabetic cardiomyopathy is not well established.
In our study, we observed that hyperglicemia or hypercholesterolemia 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). Unexpectedly, cardiac dysfunction was less marked in diabetic rats fed with an hyperlipidemic diet suggesting an adaptative response to injury of diabetic heart in the presence of hyperlipidemia. Growing evidence shows that the development of left ventricular dysfunction in diabetes is induced by myocardial injury which is characterized by mitochondrial dysfunction and altered myocardial metabolism. In particular, oxidative stress appears to play a very important role in tissue damage as we observed in diabetic rats fed with normocaloric diet showing an overexpression of myocardial NADPH oxidase compared to control. On the other hand, the concomitant presence of both pathological conditions in diabetic rats fed with hyperlipidemic diet induced a down-expression of myocardial NADPH oxidase compared to diabetic rats not affected by hyperlipidemia and improved mitochondrial function. This latter effect was also accompanied by a different modulation of cardiac remodeling, mediated by matrix metalloproteinases, in response to oxidative stress injury induced by diabetes. Further investigations are needed to better clarify mechanisms involved in diabetes-induced mitochondrial dysfunction. Our results highlight the importance to prevent free radicals-induced diabetic cardiomyopathy and represent a new insight in the identification of new pharmacological targets in order to counteract oxidative damage and to improve cardiac dysfunction in diabetes.

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