NITRIC OXIDE AND MITOCHONDRIAL BIOGENESIS: PATHOPHYSIOLOGICAL RELEVANCE IN THE METABOLIC SYNDROME DEVELOPMENT

Enzo Nisoli and Michele O. Carruba

Center for Study and Research on Obesity, Integrated Laboratories Network, Department of Pharmacology, Chemotherapy and Medical Toxicology, School of Medicine, University of Milan, Milan, Italy

Metabolic syndrome is a multifactorial, chronic disorder that has reached epidemic proportions in most industrialized countries and is threatening to become a global epidemic. Metabolic sindrome is defined by visceral fat accumulation, accompanied by insulin resistance or type 2 diabetes mellitus, hypertension, hypertriglyceridemia, high uremic acid levels, and low high density lipoprotein (HDL) cholesterol. It is now considered a major cardiovascular risk factor in a large percentage of population in worldwide. Metabolic syndrome is a particularly challenging clinical condition to treat because of its complex molecular basis. Impaired cell metabolism has been suggested as a putative pathophysiological process leading to the different clinical features of the syndrome. In particular, a defective oxidative metabolism seems to be involved in visceral fat gain and in the insulin resistance development in skeletal muscle. This suggests that mitochondrial function may be impaired in the metabolic syndrome. Recently, we have reported that mitochondrial biogenesis and function are increased by nitric oxide in various cell types and tissues. Moreover, we found that endothelial nitric oxide synthase null mutant mice are affected by visceral fat accumulation, high blood pressure, and insulin resistance with concomitant reduction of mitochondrial content in several tissues, including adipose tissue and skeletal muscle. Interestingly, increasing evidence suggest that the gaseous messanger might be considered a cellular metabolic sensor. This implies that a detective nitric oxide production might be linked to cell metabolism dysfunction. Here we summarize our view on this issue and propose a novel pathophysiological hypothesis for metabolic syndrome with putative therapeutic implications.