Dysfunctions of vascular endothelium play a role in most human diseases as a primary cause or a result of organ damage. Among them insulin resistance and diabetes seem to be the most common. Untreated endothelial impairment leads to serious and life-treating cardiovascular complications such as myocardial infarction, nephropathy and retinopathy particularly often in diabetic patients. Despite intensive investigations mechanisms underlying endothelial dysfunction as well as natural protective processes are not explained satisfactorily. Better understanding of them may be important for development of new efficient therapies. However, in this project we propose basic studies which aim at explanation of one of potential mechanisms activated as a endothelial response to stress resulted from insulin resistance, inflammation or exposition of endothelial cells to other agents affecting proper endothelial function. Recently, literature data point-out N-nicotinamide methyltransferase (NNMA) as an important player in the regulation of energy metabolism of various cells. This enzyme catalyzes transfer of methyl group from S-adenozylmethionine to nicotinamide (NA) producing 1-methylnicotinamide (MNA). NA is a precursor of NAD^+, thus its methylation may reduce cellular pool of nicotinamide adenine dinucleotides and affect cellular energy metabolism. Previously, it was found that exogenous MNA exhibits vasoprotective effect, while there are no data concerning similar effects of MNA synthesized endogenously in endothelial cells. However it is well documented that activation of NNMA results in a stimulation of other enzymes called sirtuins. Sirtuins catalyse deacetylation of many proteins, thus may result in modification of their biological function. Moreover, it was also found that sirtuins prevent blood clotting and inflammation, and stimulate mitochondrial energy metabolism. Thus we hypothesize that increase of NNMT activity in endothelial cells have an vasoprotective effect because of stabilization/activation of sirtuins and modification of mitochondrial metabolism. The aim of this project is to verify this concept. Although this grant proposal concerns important medical problem, the experiments we planned are not to develop a new therapeutic approach. These investigations are to understand a biochemical mechanisms underlying protective NNMT-action. In our studies we will use cell lines unaffected and treated with palmitate to induce insulin resistance, with TNFalpha to induce inflammatory response and with other stimuli affecting proper endothelial function in a way reflecting *in vivo* occurring processes. We will investigate amount and activity of NNMT and sirtuins. Moreover, intensity of oxygen consumption and many other mitochondrial and cellular parameters will be of our interest. Moreover, we will assess typical properties and functions of endothelial cells such as cytokine synthesis and release, and expression of adhesion molecules. It allows defining endothelial phenotype under stress conditions. Endothelial cells are not homologues and their phenotype depends on their location in the organisms. Thus the most important results obtained for one cell line will be verified with the use of endothelial cells derived from other organs. We expect that coordinated efforts of two groups, having complementary expertise in studies on metabolism and biology of endothelial cells allow accomplishing the main goal of this project and explain one of mechanisms underlying serious and commonly occurring pathology.