Exploring the cardiovascular protective effects and molecular mechanism of modulating mitochondrial quality of 5-Methoxytryptophan in ischemic cardiomyopathy

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The development of innovative therapeutic strategies to mitigate inflammation and oxidative stress after myocardial infarction (MI) remains an urgent clinical challenge. 5-Methoxytryptophan (5-MTP), a tryptophan metabolite synthesized and released from human endothelial cells, has demonstrated potent anti-inflammatory properties in both in vitro and in vivo models. In cardiac protection, 5-MTP has been shown to rescue rat cardiomyocytes from H_2O_2-induced oxidative damage.

We established a rat MI model via permanent ligation of the left anterior descending artery to investigate the therapeutic potential of 5-MTP. Intraperitoneal injection of 5-MTP at 30 min and 24 h post-ligation significantly reduced infarct size and preserved left ventricular (LV) systolic function. Levels of reactive oxygen species (ROS), assessed by luminol and lucigenin chemiluminescence, were markedly elevated in the infarcted area but returned to baseline upon 5-MTP treatment. Western blot analysis further demonstrated that 5-MTP abrogated the upregulation of NOX1, NOX2, and NOX4, key enzymes involved in ROS generation, and attenuated endothelin-1 expression. In addition, mitochondrial integrity, crucial for ROS homeostasis, was preserved as 5-MTP treatment restored TOMM20 protein expression and maintained mitochondrial antioxidant enzymes, superoxide dismutase 2, and peroxiredoxin 3.

Given that mitochondrial dysfunction is a hallmark of cardiovascular diseases, we further investigated 5-MTP's cardioprotective mechanisms in cultured human ventricular cardiomyocytes (HCMs) and HL-1 cardiac cells under oxidative stress. Our findings revealed that 5-MTP upregulates PINK1, a pivotal regulator of mitochondrial homeostasis, and that PINK1 knockdown attenuates the protective effects of 5-MTP against cardiomyocyte apoptosis. 5-MTP also reduced mitochondrial superoxide production, preserved mitochondrial membrane potential, and maintained mitochondrial network integrity. Notably, 5-MTP inhibited the phosphorylation of dynamin-related protein 1, a key factor in mitochondrial fission, stabilizing mitochondrial dynamics.

Further analyses showed that 5-MTP attenuates oxidative stress-induced mitophagy and reduces mitochondrial Parkin recruitment and mitophagy detection dye fluorescence. Additionally, restoration of AKT phosphorylation and reduced mitochondrial Bax translocation suggest that 5-MTP exerts mitochondrial protection beyond the PINK1/Parkin pathway. In our ischemic cardiomyopathy rat model, 5-MTP treatment not only enhanced PINK1 expression but also reduced pro-apoptotic Bax levels, corroborating its cardioprotective effects.

Our findings demonstrate that 5-MTP mitigates mitochondrial dysfunction by integrating the roles of PINK1, AKT, and Bax, offering potential as a therapeutic agent to enhance cellular resilience against oxidative stress-induced mitochondrial damage. Further molecular studies and pharmacokinetic optimizations are warranted to advance 5-MTP toward clinical applications in ischemic heart disease.