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News & Comments

Combination Therapy is a Better Choice to Protect the IR Heart

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Obesity is a worldwide epidemic that has major repercussions on the cardiovascular system, predisposing to ischemic heart disease. The fundamental processes causing this resistance to cardioprotection have not been addressed and require additional investigation. In patients with myocardial infarction, IR-induced myocardial arrhythmias are common clinical symptoms, and their severity and frequency increase in the context of hypercholesterolemia and obesity. Obese persons' adipose tissue has been identified as a significant generator of Reactive Oxygen Species (ROS). Overproduction of ROS may contribute to the development of increased lipid peroxidation and oxidative stress, resulting in electrolyte and ionic equilibrium imbalances and dysregulation of critical organelles such as mitochondria. It has been claimed that melatonin's efficacy rises when paired with Dipeptidyl Peptidase inhibitors in metabolic and sleep disorders.

As a result of the beneficial potentials of both melatonin and sitagliptin, the purpose of this study was to determine whether postconditioning with melatonin and sitagliptin can confer significant antiarrhythmic effects following myocardial IR injury in obese rats by modulating NO production, mitochondrial function, and oxidative stress and whether the mitoKATP channels are involved in the cardioprotective effect of melatonin/sitagliptin combination.

The study was carried out at the Department of Emergency, Capital Medical University, China. 36 male Sprague-Dawley rats (25020 g) were enrolled in this study and housed in the animal room under typical conditions of a 12-hour light/dark cycle at 222EC and 50-55 percent humidity. Novartis supplied the sitagliptin (Basel, Switzerland). Jiancheng Bioengineering Institute provided the assay kits for Creatine Kinase (CK), Malondialdehyde (MDA), catalase, Superoxide Dismutase (SOD), and Glutathione Peroxidase (GPX). The obese rats were put into six groups of six animals each. During the IR studies, three gold electrodes were placed on the rats' right and left hands, as well as their right foot, to record electrocardiographic traces on the axis lead. At the end of the reperfusion period, blood samples were taken from the hearts of rats, and the hearts were then removed. To measure mitochondrial ROS, mitochondrial supernatants were treated for 30 min at 37 °C with 2 M Dichlorodihydro-Fluorescein Diacetate (DCFDA) dye. The mitochondrial supernatants were suspended in 2 mL of warmed phosphate-buffered saline containing 2 L of JC^{-1} and incubated in the dark for 30 min at 37 °C. The information was presented as Mean SD.

Melatonin alone reduced the number and timing of arrhythmias considerably, whereas sitagliptin did

not affect the number of PVC and VT or the length of VT. However, when compared to the IR group, the combination of melatonin and sitagliptin considerably and more efficiently reduced all arrhythmias. Following IR induction in obese rats, the incidence of VT and VF, as well as the severity (scoring) of arrhythmias, was significantly increased ($p<0.001$). In obese rats, myocardial CK was dramatically raised after IR injury, and melatonin and sitagliptin treatment greatly inhibited the IR-induced increase in CK release. In obese rats, myocardial CK was dramatically raised after IR injury, and melatonin and sitagliptin treatment greatly inhibited the IR-induced increase in CK release. To assess oxidative stress, intracellular quantities of MDA, the major marker of lipid peroxidation, and catalase, SOD, and GPX, the key endogenous antioxidant enzymes, were examined. Melatonin did not impact catalase alone; however, it did lower MDA ($p<0.05$) and boost SOD and GPX ($p<0.05$) when compared to the IR group. Furthermore, sitagliptin alone did not affect MDA, catalase, or GPX levels, but only elevated SOD levels ($p<0.05$). Interestingly, the combined effects of melatonin and sitagliptin on MDA decrease and catalase increase were considerably stronger than their administration ($p<0.05$). The Griess method was used to estimate myocardial NO levels in experimental groups by measuring the quantities of Nitric Oxide metabolites (NOx). The NOx level of the myocardium was dramatically reduced in the IR group in comparison to the control group ($p<0.001$).

This study found that preconditioning obese rats with melatonin and sitagliptin was advantageous. IR-induced ventricular arrhythmias are cardioprotective. Although their protective benefits in obese rats were inconsistent, their combination therapy was a superior technique for reducing all ventricular arrhythmias, suppressing oxidative stress, increasing NO production, and improving mitochondrial function.

JOURNAL REFERENCE

Wang, L. and C. Liu, 2022. Melatonin plus sitagliptin reduces ischemia/reperfusion-induced myocardial arrhythmias through mitochondrial K-ATP channels in obese rats. Int. J. Pharmacol., 18: 657-666.

KEYWORDS

Cardio protection, mitochondria, obesity, melatonin, DPP4-inhibitor, arrhythmia