3, 4-dihydroxyl-phenyl lactic acid restores NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10 expression to ameliorate cardiac reperfusion injury

Ke He¹,¹, Xiao-Yuan Yang¹,², Na Zhao¹,³, Yu-Ying Liu¹,³, Bai-He Hu¹, Kai Sun¹, Xin Chang¹, Xiao-Hong Wei¹, Jing-Yu Fan¹,³, Jing-Yan Han¹,³

¹) Tasty Microcirculation Research Center, Peking University Health Science Center, Beijing 100191, China
²) Department of Integration of Traditional Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing 100191, China

Background: Protection of ischemia/reperfusion (I/R) induced myocardial injury remains a challenge for clinician. 3, 4-dihydroxyl-phenyl lactic acid (DLA) is a major ingredient of cardiotoxic pills6, a undergoing phase III clinical trials drug for treatment of cardiovascular diseases in FDA in USA. However whether DLA exerts protective role against I/R and the intracellular target for DLA action remains unclear.

Methods and Results: Male Sprague-Dawley (SD) rats were subjected to left descending artery occlusion for 30 min, followed by reperfusion with or without DLA administration for 90 min. Results showed DLA reduced infarct size, diminished myocardial apoptosis and ameliorated impaired cardiac function and myocardial blood flow (MBF) after I/R. The results of 2-D fluorescence difference gel electrophoresis and activity assay kit revealed that DLA prevented from decrease in NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, 10 (NDUFA10) expression, one of the subunits of Complex I, blunted the impairment of Complex I activity and mitochondrial function. To find the target of DLA, the binding affinity of Sirtuin 1 (SIRT1) to DLA and DLA derivatives with replaced two phenolic hydroxyls were detected using surface plasmon resonance and bilayer interferometry. The observed results demonstrated DLA was able to bind to SIRT1, depending on phenolic hydroxyl.

Conclusions: The present study demonstrated the capability of DLA to bind to and activate SIRT1, which plays an essential role in the cardioprotective effects of DLA. Preserved SIRT1 activity by DLA is responsible for the restored NDUFA10 protein and improved mitochondrial function, eventually leading to repressed infarct size and apoptosis, preserved cardiac function and MBF after I/R.

Comparison of peripheral vascular resistance based on macro- and micro-circulatory responses by Poilleuille’s law

Kazuhiro Yokokawa, Saki Hamashima, Masahiro Shibata

Department of Bio-Science and Engineering, Shibaura Institute of Technology

The total peripheral vascular resistance (TPR) is essential index in the cardiovascular system, since both the systemic blood pressure and blood flow could be determined by the changes of TPR. Such important index, the TPR cannot be measured directly, so Darcy’s law would be applied to determine TPR. On the other hand, vascular flow resistance would be mainly controlled by the contraction or dilation of small arteries and arterioles, existing at the upstream of capillaries. Regarding the single small artery and the arteriole, the vascular flow resistance (R) could be represented as R=8 μL/π r⁴, called Poilleuille’s law (μ: viscosity, r: vessel radius L: vessel length=constant). In addition, the major contribution of these vascular resistances would be caused by the resistance vessels in the skeletal muscle, since the blood flow in skeletal muscle dramatically changes from resting to excise, approximately 20 times increases. These facts suggest the TPR would be determined by the levels of contraction and dilation in skeletal muscle arterioles. In the present study, we tried to investigate in macro- and microcirculation whether the TPR can be estimated from the diameter changes of single arteriole in the skeletal muscle using Dalcy and Poilleuille’s laws. Wister rats (180 - 400g b.w.) were anesthetized, and carotid artery and vein were cannulated for the blood pressure measurement and administration of L-NAME, inhibitor of NOS production, respectively. The observation of microcirculation was carried out in the cremaster muscle by intravitalmicroscopy. The TPR was calculated by the changes in the blood pressure during L-NAME caused vasoconstriction based on the Dalcy’s law, while the R was calculated by the changes in the arteriolar diameter based on the Poilleuille’s law. The TPR and R were increased 23.9±7.7% and 23.5±8.7% from control to L-NAME caused vasoconstriction, respectively. These results suggest the Poilleuille’s law can apply to estimate the TPR in vivo microcirculation. Furthermore, it has been confirmed the TPR would be regulated mainly by the contraction and dilation of the skeletal muscle arterioles.