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Mechanism and consequences of the shift in cardiac arginine metabolism following ischaemia and reperfusion in rats

Schreckenberg R., Weber P., Cabrera-Fuentes H., Steinert I., Preissner K., Bencsik P., Sárközy M., Csonka C., Ferdinandy P., Schulz R., Schlüter K.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© Schattauer 2015. Cardiac ischaemia and reperfusion leads to irreversible injury and subsequent tissue remodelling. Initial reperfusion seems to shift arginine metabolism from nitric oxide (NO) to polyamine formation. This may limit functional recovery at reperfusion. The hypothesis was tested whether ischaemia/reperfusion translates such a shift in arginine metabolism in a tumour necrosis factor (TNF)-α-dependent way and renin-angiotensin system (RAS)-dependent way into a sustained effect. Both, the early post-ischaemic recovery and molecular adaptation to ischaemia/reperfusion were analysed in saline perfused rat hearts undergoing global no-flow ischaemia and reperfusion. Local TNF-α activation was blocked by inhibition of TNF-α sheddase ADAM17. To interfere with RAS captopril was administered. Arginase was inhibited by administration of Nor-NOHA. Long-term effects of ischemia/reperfusion on arginine metabolism were analysed in vivo in rats receiving an established ischaemia/reperfusion protocol in the closed chest mode. mRNA expression analysis indicated a shift in the arginine metabolism from NO formation to polyamine metabolism starting within 2 hours (h) of reperfusion and translated into protein expression within 24 h. Inhibition of the TNF-α pathway and captopril attenuated these delayed effects on post-ischaemic recovery. This shift in arginine metabolism was associated with functional impairment of hearts within 24 h. Inhibition of arginase but not that of TNF-α and RAS pathways improved functional recovery immediately. However, no benefit was observed after four months. In conclusion, this study identified TNF-α and RAS to be responsible for depressed cardiac function that occurred a few hours after reperfusion.

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