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Cholesterol-enriched diet inhibits cardioprotection by ATP-sensitive K\textsuperscript{+} -channel activators cromakalim and diazoxide

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It has been previously shown that hyperlipidemia interferes with cardioprotective mechanisms. Here, we investigated the interaction of hyperlipidemia with cardioprotection induced by pharmacological activators of ATP-sensitive K\textsuperscript{+} - (K\textsubscript{ATP}) channels. Hearts isolated from rats fed a 2% cholesterol-enriched diet or normal diet for 8 wk were subjected to 30 min of global ischemia and 120 min of reperfusion in the presence or absence of K\textsubscript{ATP} modulators. In normal diet-fed rats, either the nonselective K\textsubscript{ATP} activator cromakalim at 10\textsuperscript{-5} M or the selective mitochondrial (mito)K\textsubscript{ATP} opener diazoxide at 3 \times 10\textsuperscript{-5} M significantly decreased infarct size compared with vehicle-treated control rats. Their cardioprotective effect was abolished by coadministration of the nonselective K\textsubscript{ATP} blocker glibenclamide or the selective mitoK\textsubscript{ATP} blocker 5-hydroxydecanoate, respectively. However, in cholesterol-fed rats, the cardioprotective effect of cromakalim or diazoxide was not observed. Therefore, we further investigated how cholesterol-enriched diet influences cardiac K\textsubscript{ATP} channels. Cardiac expression of a K\textsubscript{ATP} subunit gene (Kir6.1) was significantly downregulated in cholesterol-fed rats; however, protein levels of Kir6.1 and Kir6.2 were not changed. The cholesterol diet significantly decreased cardiac ATP, increased lactate content, and enhanced myocardial oxidative stress, as shown by increased cardiac superoxide and dityrosine formation. This is the first demonstration that cardioprotection by K\textsubscript{ATP} channel activators is impaired in cholesterol-enriched diet-induced hyperlipidemia. The background mechanism may include hyperlipidemia-induced attenuation of mitoK\textsubscript{ATP} function by altered energy metabolism and increased oxidative stress in the heart.