Sex differences in myocardial infarct size are abolished by sarcolemmal K\textsubscript{ATP} channel blockade in rat

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Submitted 8 December 2005; accepted in final form 24 January 2006

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23/1000 to 52/1000 of the ZAR (P < 0.001). To the contrary, infarct size, after the addition of HMR-1098 during the reperfusion period only, was not different from that of control hearts (23 ± 3% of the ZAR; P = NS). Infarct size after 3 h of HMR-1098 administration was not statistically different from infarct size when HMR-1098 was administered immediately before ischemia (42 ± 4 vs. 52 ± 3% of the ZAR, respectively; P = NS).

DISCUSSION

The majority, but not all (16, 24), of the studies performed on a wide variety of experimental animal models provide strong evidence that myocardium from females, relative to males, is intrinsically more resistant to I/R-induced tissue injury and infarction (1, 4, 7, 10, 15, 19). The data in this study corroborate these findings (Fig. 1). The reasons for the lack of complete consensus on this issue are not known, but the basis for the disparate findings may be related to the interpretive complexities associated with the use of different animals models and analytical methodologies. Additionally, it is apparent that the cellular basis for sex differences in the susceptibility of the heart to infarction is probably quite complex and to date has eluded clear description. To begin to address this issue, this study was conducted to determine the potential contribution of sarcKATP channels in sex-specific resistance to myocardial infarction.

In our earlier work (4), we found that the cardioprotection associated with female sex was accompanied by a greater protein expression of the sarcKATP channel subunits. The present study provides the first demonstration in the intact heart that blockade of sarcKATP channels during in vitro I/R abrogates the sex difference in myocardial infarct size and implicates sarcKATP channels as being required mediators of enhanced protection in female rats. Previous studies from Jovanovic’s laboratory (26) on isolated cell systems have shown that cardiocytes from female hearts expressed a greater pinacilinduced outward current and were more resistant to cellular calcium overload than cells from male hearts. A subsequent study by this group (25) indicated that 17-β estradiol increased sarcKATP channel expression (and is protective against hypoxia reoxygenation-induced cell injury) in a heart-derived H9c2 cell line and that KATP channel antagonist abolished the protection afforded by 17-β estradiol. The data presented herein provide a crucial extension of these studies in that they clearly demonstrate that the sarcKATP channel-dependent cardioprotection in females is present in the whole heart and that the temporal...
involvement of sarcK<sub>ATP</sub> channels in the cardioprotective process is most important during the ischemic, rather than the reperfusion, phase of I/R stress.

Blocking the sarcK<sub>ATP</sub> channel population in male rats had no effect on myocardial infarct size (Fig. 1). These data are consistent with a number of studies indicating that sarcK<sub>ATP</sub> channel blockade during an I/R protocol does not alter infarct size in hearts from male rats (13, 21) and support our evidence that a sex-specific difference in K<sub>ATP</sub> channel-induced protection from myocardial infarction is present. It is also noteworthy that in nonpreconditioned hearts from both male (21, 27) and female (2) rats, it has been demonstrated that the putative mitochondrial K<sub>ATP</sub> channel antagonist 5-hydroxydecanoate (5-HD) has no effect on infarct size, suggesting that mitochondrial K<sub>ATP</sub> channels do not play a central role in the sex-dependent differences in the susceptibility of the heart to myocardial infarction. This also indicates that the intrinsic, sex-dependent resistance of the heart to I/R injury is not analogous to a broad array of acquired cardioprotection models, almost all of which have been shown to be 5-HD sensitive (5, 8, 9, 14, 21–23). One notable exception is cardioprotection acquired by long-term exercise, which has recently been shown to be HMR-1098 sensitive and 5-HD insensitive (2); interestingly, this study was conducted on female rats.

Although the exact mechanisms whereby K<sub>ATP</sub> channels may provide protection in female, but not male, hearts require further experimentation, our results are intriguing in light of a very recent study by Bae and Zhang (1). These investigators found that the smaller infarct size in female hearts was related to an increased activity of protein kinases B (also called Akt) and C. Analogous to our findings (Fig. 1), inhibition of these kinases before ischemia resulted in expanded infarct size in female, but not male, hearts. Given the fact that protein kinases have been widely shown to influence the activity of myocardial K<sub>ATP</sub> channels (for review articles, see Refs. 6, 17, 20, and 28), an interesting sex-specific cascade of events incorporating receptor activation, second messenger signaling, K<sub>ATP</sub> channel phosphorylation, and, ultimately, cardioprotection may be slowly evolving. Obviously, future experiments will be needed to elucidate the specific sex differences in cellular strategies of cardioprotection.

In summary, we have shown that inhibition of sarcK<sub>ATP</sub> channels during ischemia abolishes the sex difference in infarct size, providing evidence that hearts from males and females may respond to ischemia via very different mechanisms. Given the prevalence of studies examining both paradigms of preconditioning and intrinsic protection from infarction, our hope is that further attention will be given to the sex of animals studied to further explore sex differences in the susceptibility of the myocardium to I/R injury.

ACKNOWLEDGMENTS

We thank Dr. Heinz Gogelein at Aventis Pharma, Frankfurt, Germany, for the gift of HMR-1098.

GRANTS

This work was supported by National Heart, Lung, and Blood Institute Grants HL-40306 and HL-72790 (to R. L. Moore), National Institute of Aging Institutional Training Grant AG-279 (to D. A. Brown), and the National Institutes of Health (NIH)/Howard Hughes Medical Institute Scholarship Program for Diversity (NIH-GM-066728-01; to M. S. Johnson).

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