Ageing and sarcolemmal $\text{K}_{\text{ATP}}$ channels in the heart: why we should care?

Aleksandar Jovanovic
Coronary Heart Disease

- Age-related
- Most common cause of death in the developed world
- 2.68 million people living with CHD in the UK*
- Scotland: 1 in 3 people die from heart disease
- Arteriosclerosis: disease of coronary arteries
- Clinical manifestation: stable angina → acute myocardial infarction (AMI)

* British Heart Foundation (2004)

• Similar findings have been reported in humans (Goldberg et al., 1989, Am Heart J 117: 543-549; Mariani et al., 2000, J Thorac Cardiovasc Surg 120: 660-667)
$K_{ATP}$ channels: metabolic sensors

- inhibited by ATP

- opening regulated by ADP:ATP ratio
The activation of KATP channels is cardioprotective

Necrotic tissue

Channels closed

Channels open
Sarcolemmal $K_{\text{ATP}}$ channels: structure

- heteromultimeric structure
  - 4 x Kir6.2 (channel pore) 4 x SUR2A (regulatory subunit)

(Inagaki et al., 1996 Science 270, 1166-1170)

SUR2x/Kir6.x stoichiometry: determines physiology/pharmacology

**Kir subunit**: $K^+$ permeance

**SUR subunit**: ATP/drug binding sites

Associated proteins: AK, CK, m-LDH
RT-PCR can measure Kir6.2 and SUR2A mRNA levels
Ageing has no effect on Kir6.2 mRNA levels in the heart
Ageing is associated with gender-dependent decrease of SUR2A mRNA level in the heart.
Ageing is associated with decreased levels of both Kir6.2 and SUR2A subunits in female hearts.
Patch clamp electrophysiology confirms data obtained by Western blotting.
There is no age-dependent difference in single sarcolemmal $K_{ATP}$ channel properties
Kir6.2 mRNA is expressed in excess over SUR2A mRNA in the heart
17β-estradiol (E2) increases level of SUR2A, but not Kir6.2, mRNA in rat heart embryonic H9C2 cells
17\(\beta\)-estradiol (E2) increases levels of both Kir6.2 and SUR2A subunits in H9C2 cells
Patch clamp electrophysiology confirms data obtained by Western blotting.
17β-estradiol (E2) protects H9C2 cells against hypoxia/reoxygenation (H/R) injury.
$17\beta$-estradiol (E2) regulates the activity of SUR2 promoter
Conclusion

Age-dependent loss of sarcolemmal $K_{\text{ATP}}$ channels and consequent increase in heart susceptibility to ischaemia could be due to an age-dependent changes in estrogen levels.
Acknowledgements

Harri Ranki
Sofija Jovanovic
Grant Budas
Russell Crawford
Tony Davies

Financial support: Anonymous Trust and TENOVUS-Scotland