

Ageing and sarcolemmal K_{ATP} channels in the heart: why we should care?

Aleksandar Jovanovic



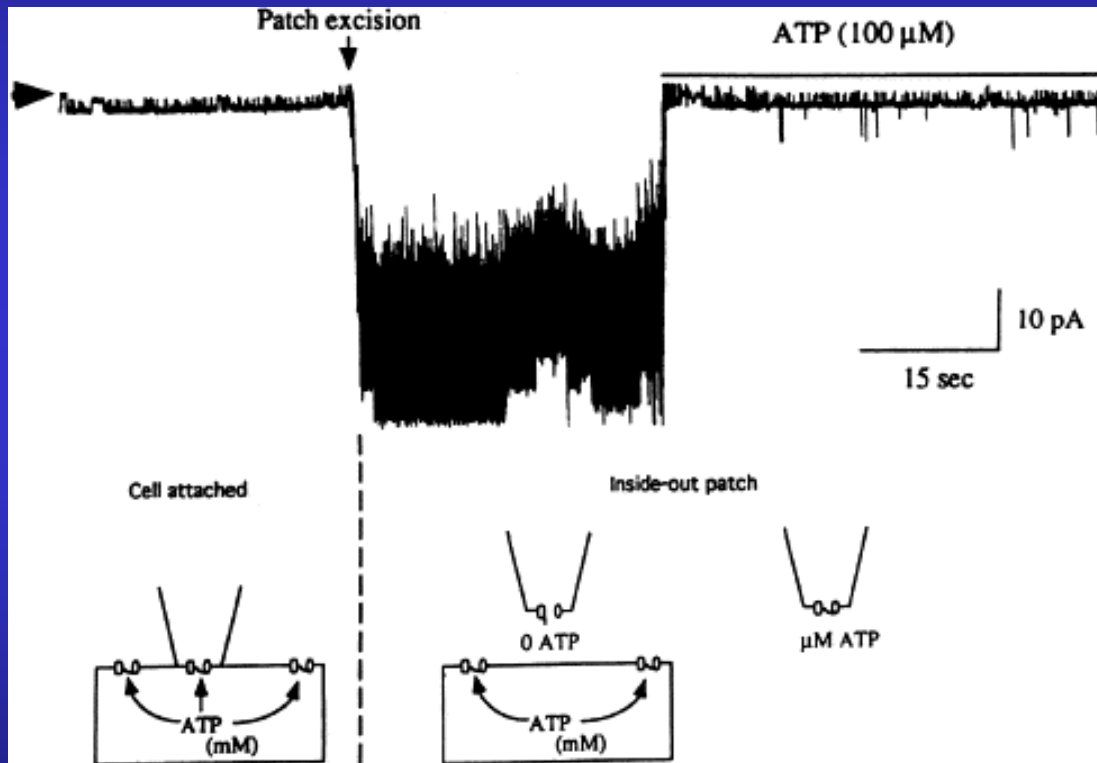
Coronary Heart Disease

- 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)

- Hearts of aged experimental animals are less tolerant to ischaemia (Lesnefsky et al., 1994, J Lab Clin Med 124: 843-851; Schulman et al., 2001, Am J Physiol 281: H1630-H1636).
- 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

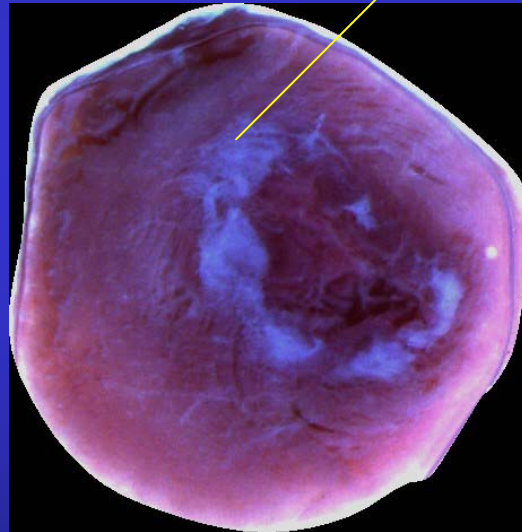


-inhibited by ATP

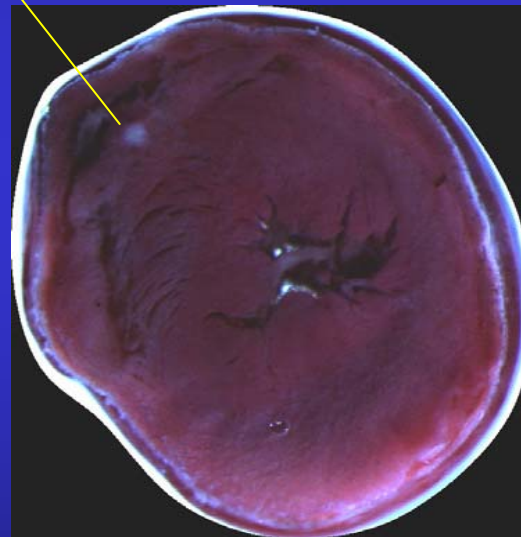
-opening regulated by ADP:ATP ratio

The activation of KATP channels is cardioprotective

Necrotic tissue



Channels closed

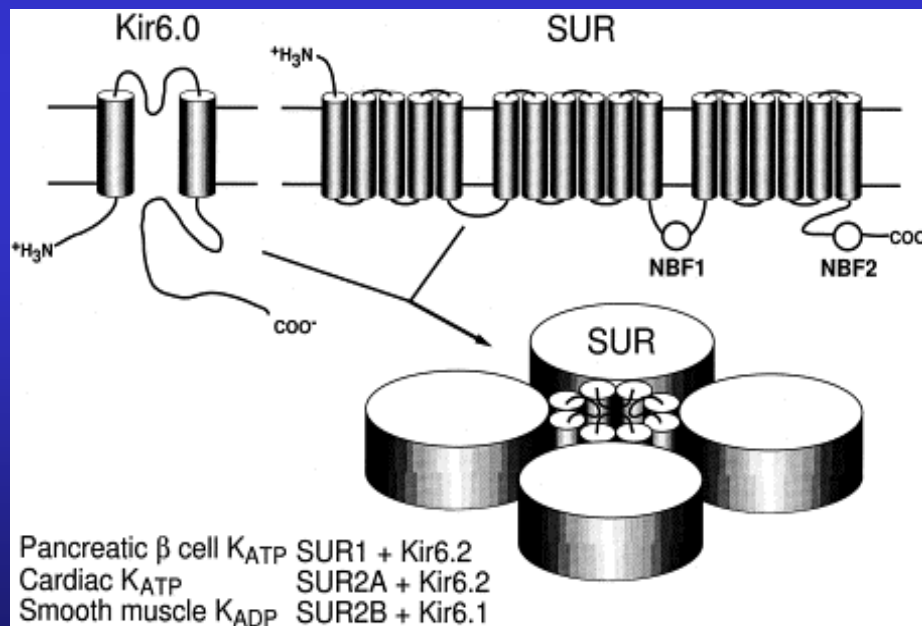


Channels open

Sarcolemmal K_{ATP} channels: structure

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

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



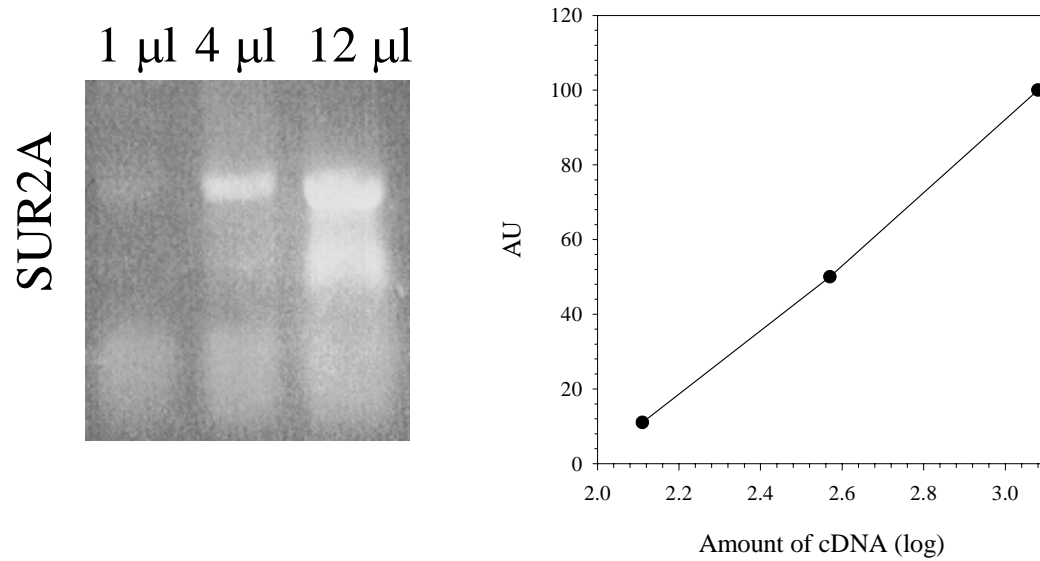
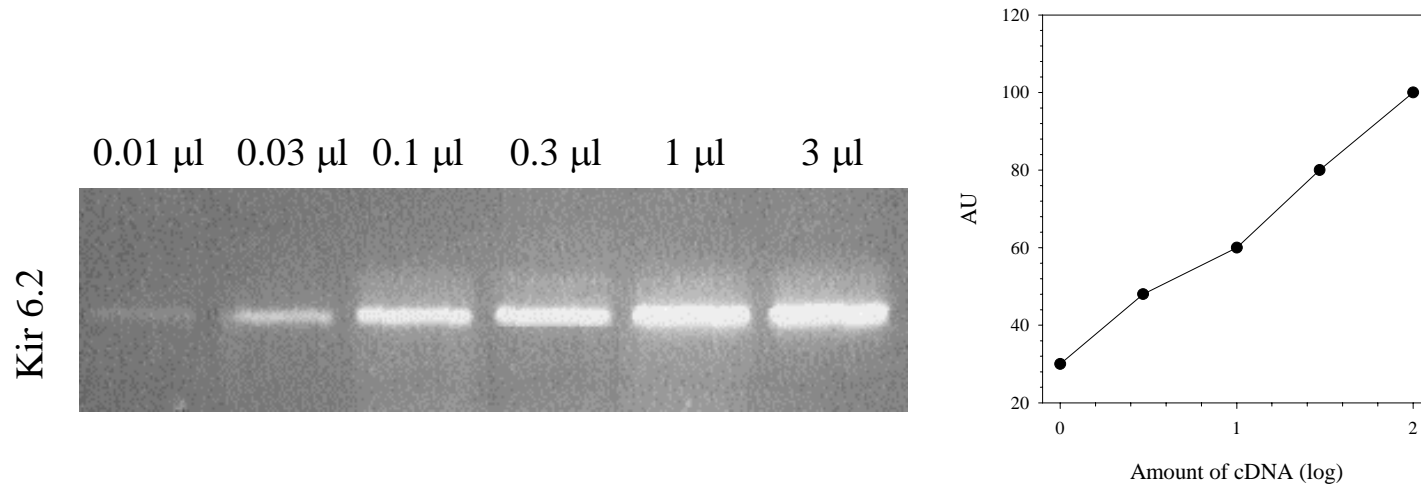
SUR2x/Kir6.x stoichiometry: determines physiology/pharmacology

Kir subunit: K^+ permeance

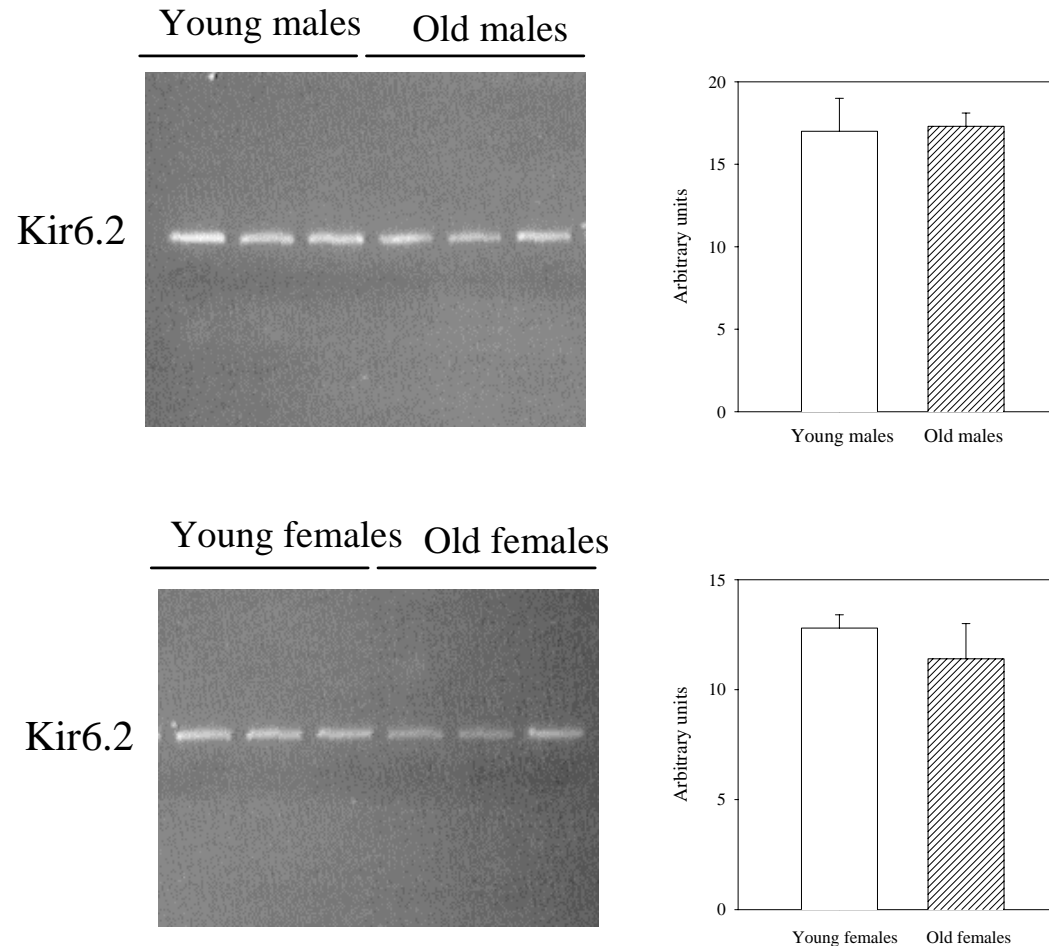
SUR subunit: ATP/drug binding sites

Associated proteins: AK, CK, m-LDH

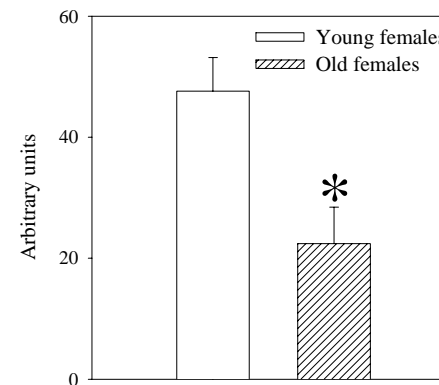
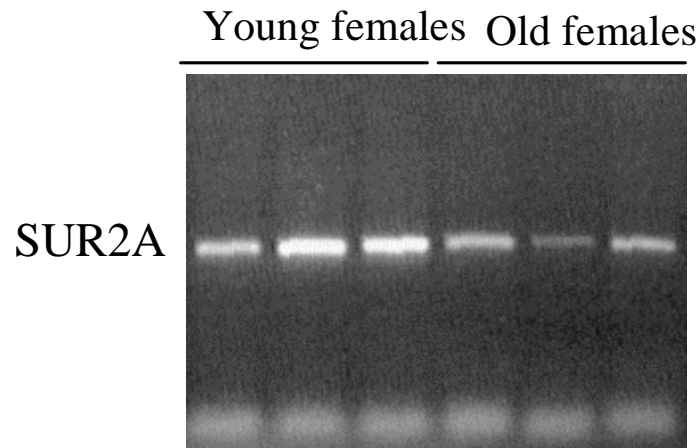
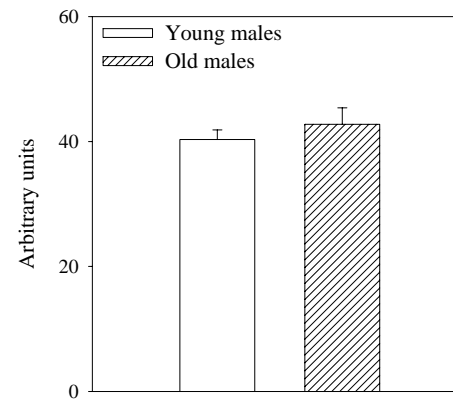
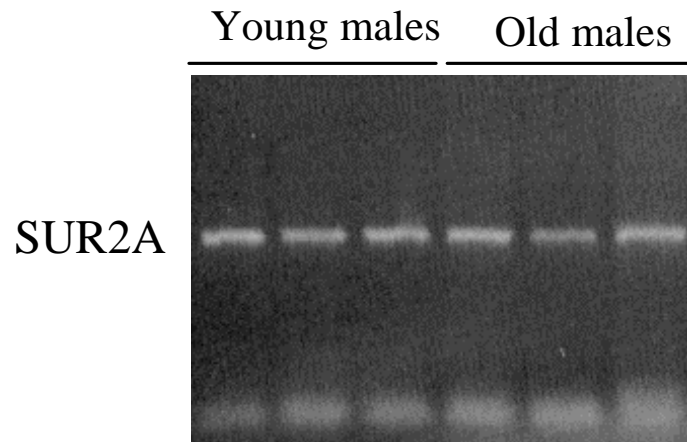
RT-PCR can measure Kir6.2 and SUR2A mRNA levels



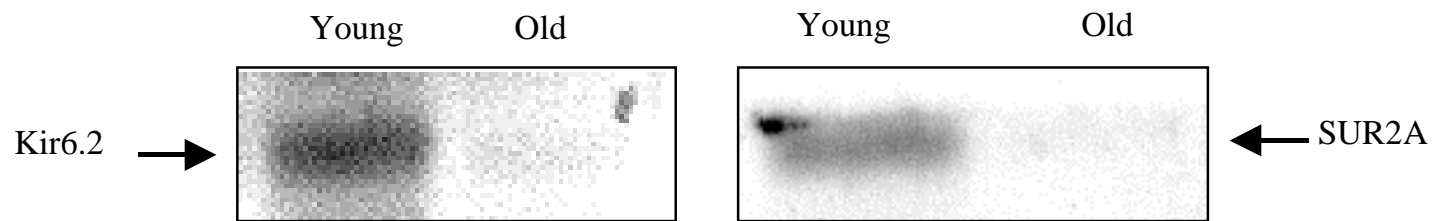
Ageing has no effect on Kir6.2 mRNA levels in the heart



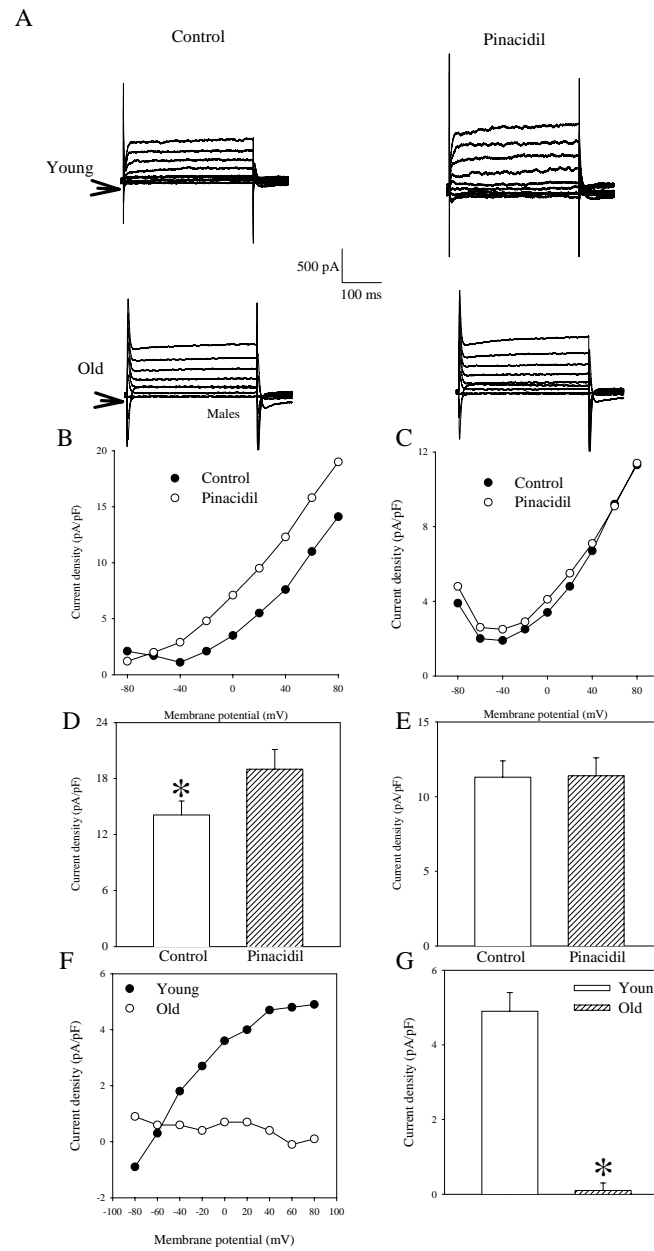
Ageing is associated with gender-dependent decrease of SUR2A mRNA level in the heart



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

Young



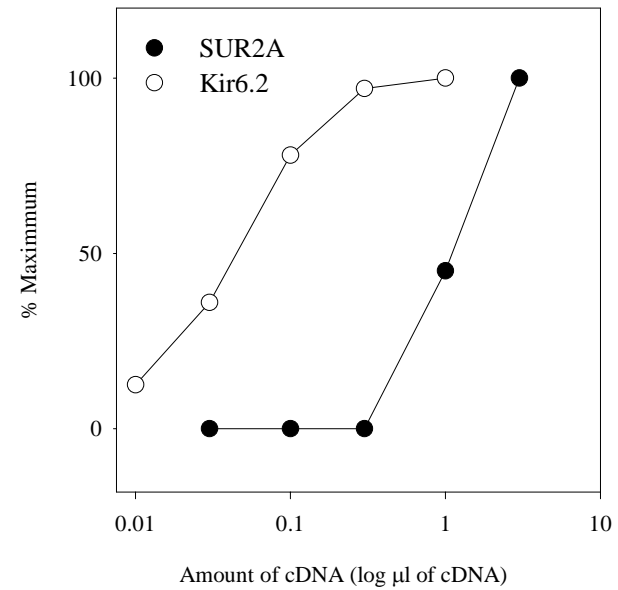
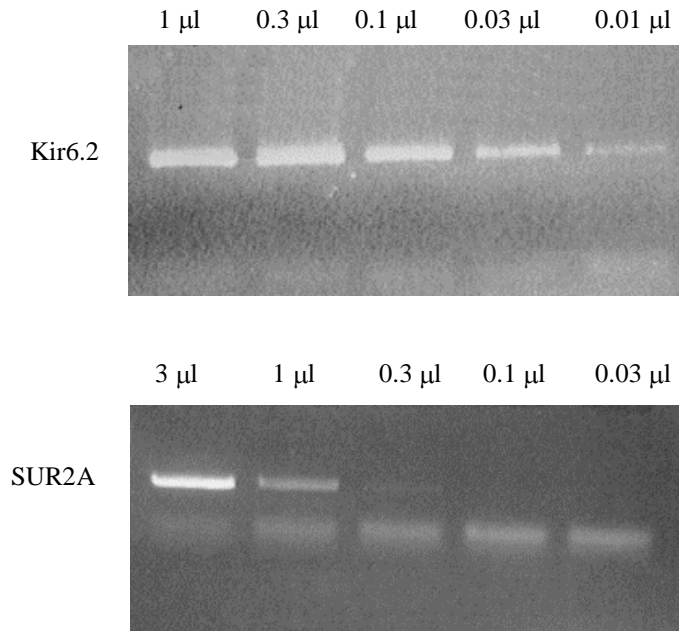
Old



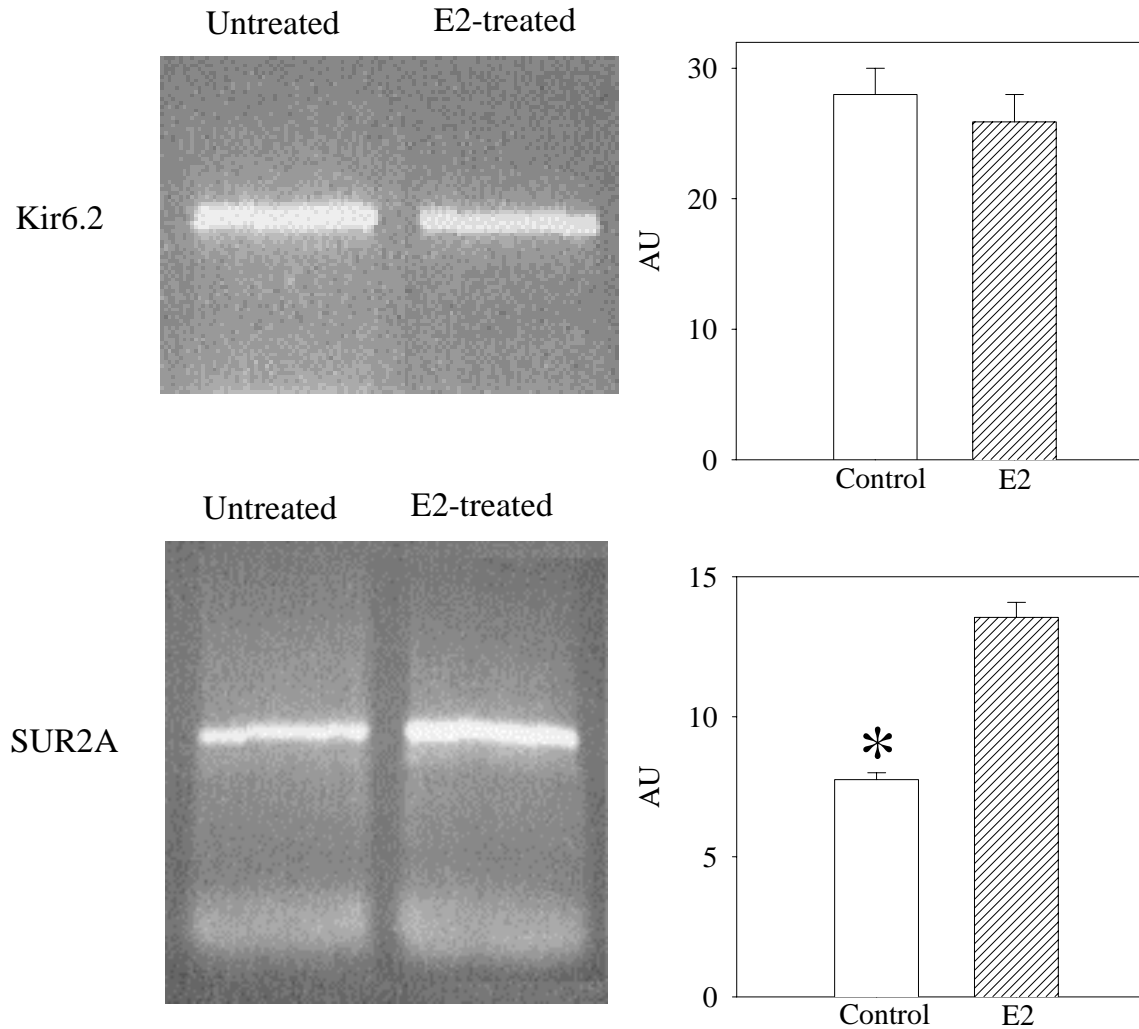
3 pA

100 ms

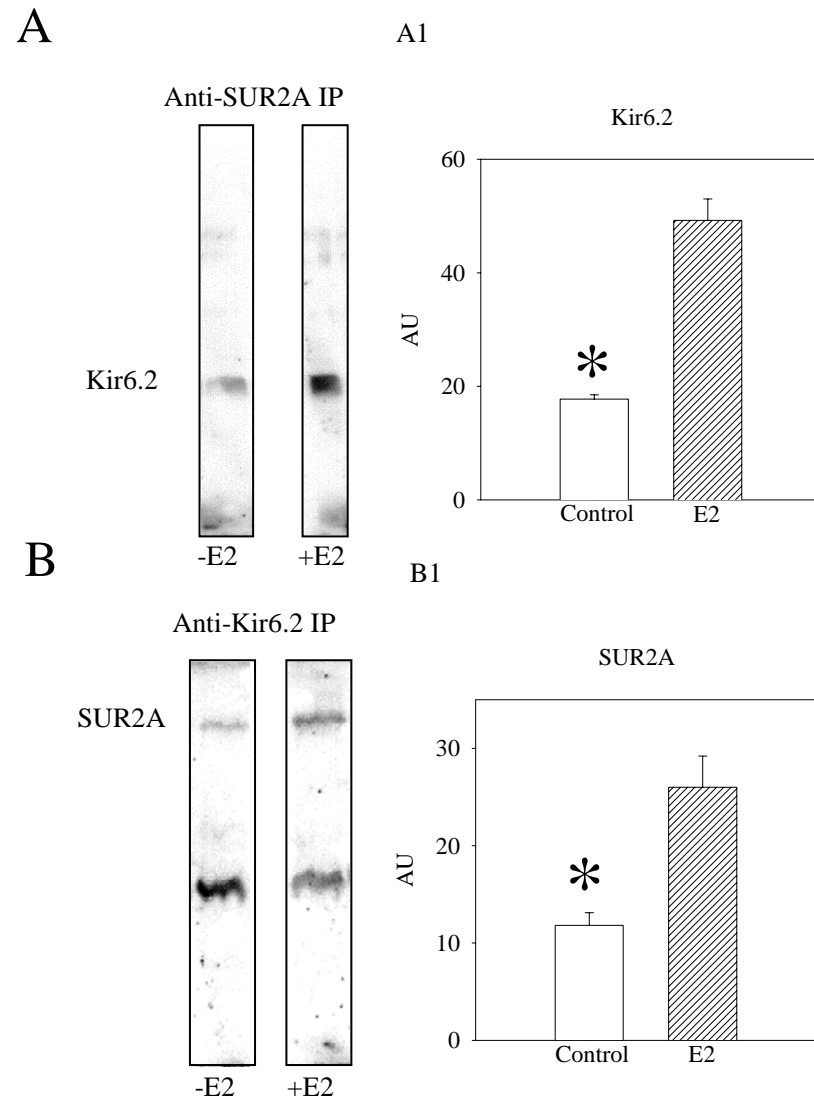
Kir6.2 mRNA is expressed in excess over SUR2A mRNA in the heart



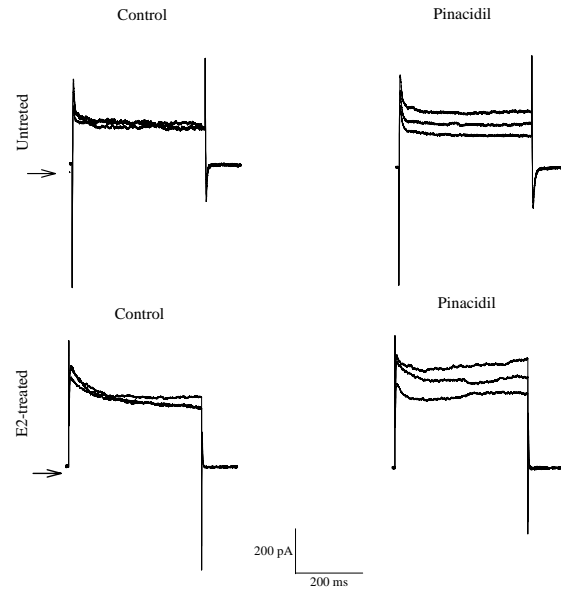
17 β -estradiol (E2) increases level of SUR2A, but not Kir6.2, mRNA in rat heart embryonic H9C2 cells



17 β -estradiol (E2) increases levels of both Kir6.2 and SUR2A subunits in H9C2 cells

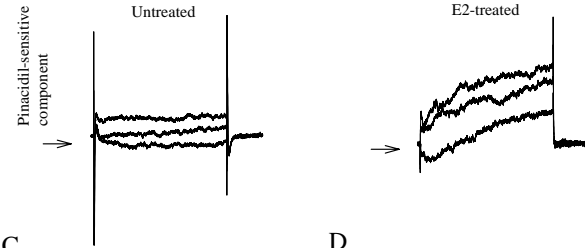


A

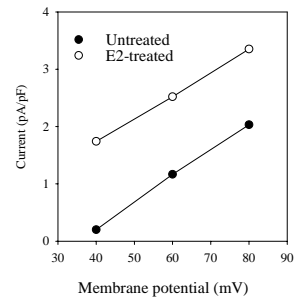


Patch clamp electrophysiology confirms data obtained by Western blotting

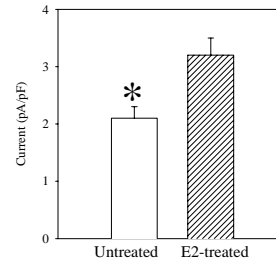
B



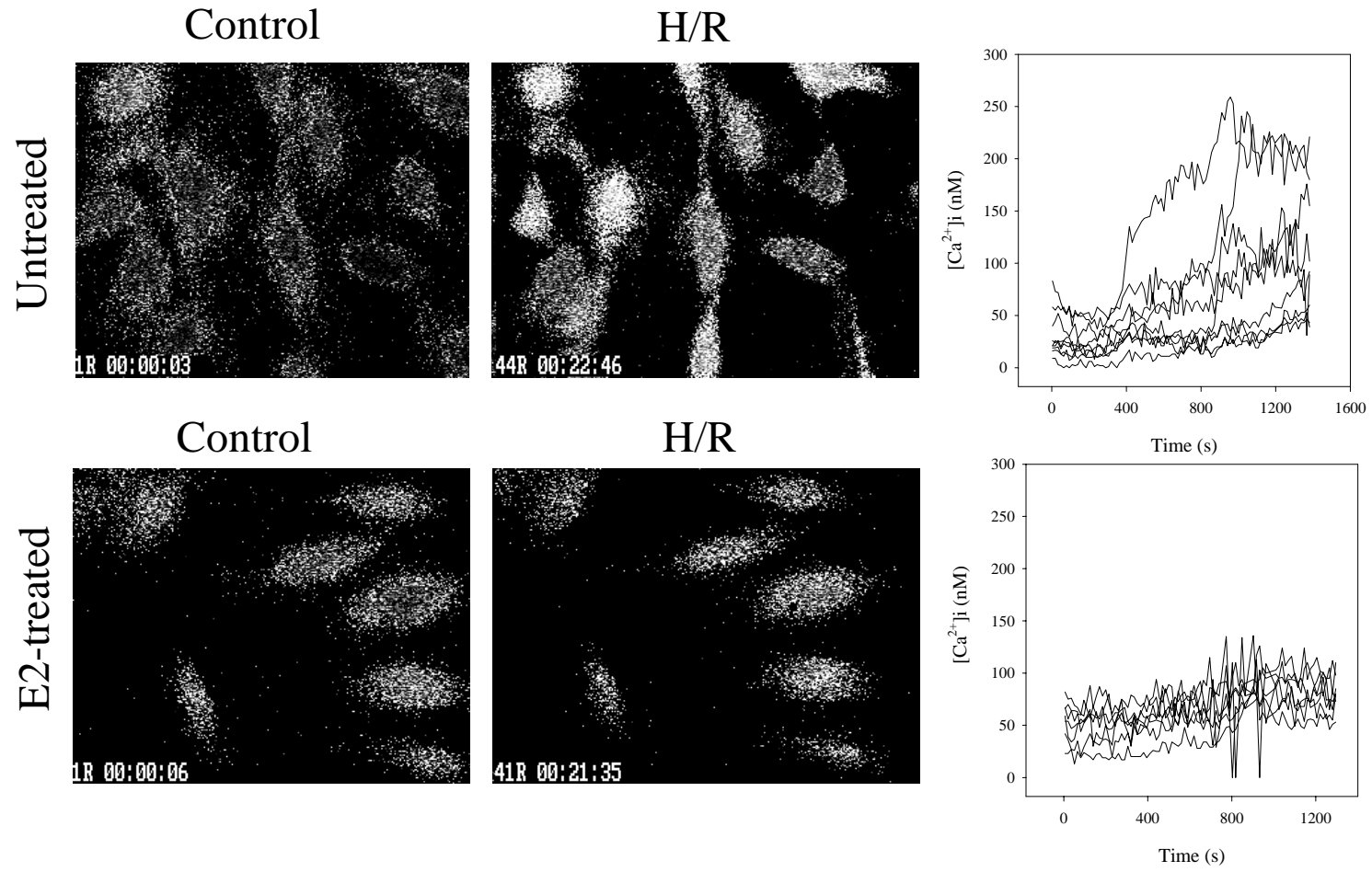
C



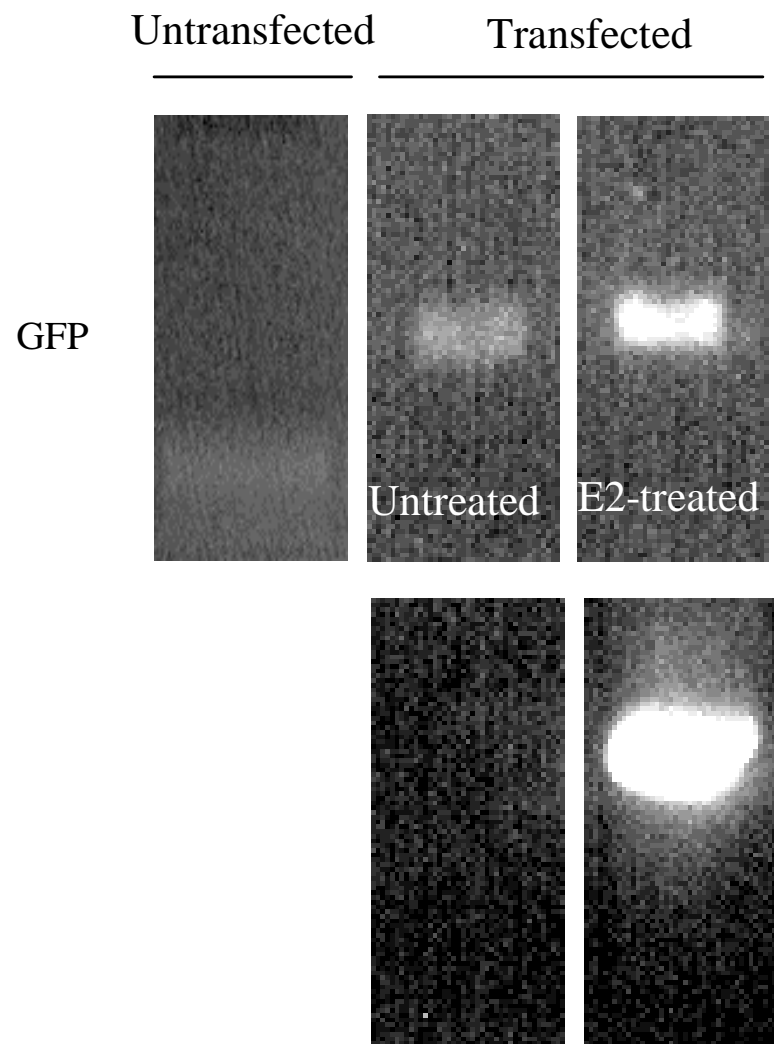
D



17 β -estradiol (E2) protects H9C2 cells against hypoxia/reoxygenation (H/R) injury



17 β -estradiol (E2) regulates the activity of SUR2 promoter



Conclusion

Age-dependent loss of sarcolemmal K_{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