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Mineralocorticoid receptor blockade prevents hyperglycaemia aggravated RAGE expression during myocardial infarction

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Diabetic patients continue to have 2-4-fold increased risk of short- and long-term mortality after acute myocardial infarction (AMI), with hyperglycemia consistently and independently predicting complications. Although not defined, a possible mechanism for hyperglycemia-aggravated cardiac damage and remodeling is augmentation of increased receptor for advanced glycation end products (RAGE), precipitated during myocardial ischemia reperfusion (I-R). Mineralocorticoid receptor (MR) antagonists reduce morbidity and mortality, although mechanism(s) not fully defined. We tested the hypothesis that MR blockade would intercept hyperglycemia-aggravated RAGE expression and reduce reperfusion injury.

Methods: Male Sprague Dawley rats (SD) and obese Zucker rats (ZDF) were anesthetized and hearts isolated and subjected to regional ischemia (30min) followed by reperfusion (2.5hr) *ex vivo*. For acute hyperglycemia, 22 mM glucose was perfused 15 min. prior to inducing ischemia and throughout reperfusion. MR antagonist spironolactone (SP, 1 μM) was added to perfusate and maintained throughout reperfusion.

Results: I-R activated RAGE expression [10.9 x 105 ± 1.7 (N=4) vs 2.9 x 105 ± 0.7 (N=4) (sham I-R), $p<0.05$], which was significantly exacerbated by acute hyperglycemia [25 x 105 ± 2.5, N=4, $p<0.05$]. Changes with acute hyperglycemia were of similar magnitude to chronic hyperglycemia in the ZDF rats [26.9 x 105 ± 2.8, N=4, $p<0.05$]. Immunoblotting confirmed increased RAGE protein expression. These changes correlated with significantly larger infarct size in the hearts from ZDF rats (49 ± 1%, N=7) and acute hyperglycemia (58 ± 2%, N=8) compared with control rats (39 ± 2%, N=8, $p<0.05$). Acute exposure to SP attenuated infarct area and RAGE expression in the hearts of both ZDF rats (43 ± 2%, N=5, $p<0.05$) and acute hyperglycemia (45± 2%, N=7, $p<0.05$).

Conclusion: Our results indicate that even short periods of hyperglycemia aggravate cardiac damage by activating RAGE. Addition of MR blockade prevented activation of RAGE and attenuated infarct size. This confirms results of the large clinical studies where MR blockade had benefit in patients with diabetes.

Biography

Anastasia Susie Mihailidou is a cardiovascular clinical scientist, graduating with a Ph.D. in Pharmacology from University of Sydney in 1988. She is currently Clinical Senior Lecturer for Sydney Medical School, University of Sydney and Senior Hospital Scientist at Royal North Shore Hospital. Anastasia has both clinical and basic research interests as Director of the Ambulatory Blood Pressure Monitoring Service for a major Tertiary Referral Centre and Head of the Cardiovascular & Hormonal Research Laboratory. Her research focus is regulation of aldosterone/mineralocorticoid receptors in the heart and has made a significant contribution to understanding the role of corticosteroid hormones (and antagonists). She was the first to show aldosterone has both rapid and sustained effects on regulation of sodium transport in the heart, with increased levels of intracellular sodium. These findings have generated great interest, leading to award of the Pfizer Prize for best research at the International Society of Hypertension (2002). Her current research focus is to determine the role of aldosterone and mineralocorticoid receptors in diabetes.

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