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Mineralocorticoid receptors in myocardial infarction – No good, just bad and ugly

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Coronary heart disease remains the most prominent single cause of death despite advances in clinical care. Restoration of blood flow to the myocardium following ischemia induces reperfusion injury. Conditional knockout mice have identified central roles for mineralocorticoid receptor (MR) activation in promoting reperfusion injury and hypertension. These studies are born out by large clinical trials showing MR antagonists reducerehospitalisation/mortality rates and slows progression to heart failure. However, the mechanism for these effects is not clearly delineated and made more contentious by the recent identification of GPR30 as an aldosterone (Aldo) receptor. Cell permeable (Aldo) and impermeable (Aldo-PEG) ligands were used to identify the receptor that promotes reperfusion injury. Aldo-PEG activated only GPR30 while Aldo activated both MR and GPR30. Aldoincreased infarct size and aggravated apoptosisin *ex vivo* reperfusion injury whereas Aldo-PEG had no effect. These data indicate that GPR30 activation is insufficient to promote reperfusion injury and that activation of MR are required. Aldo not only alters transcription but also mediates non-genomic pathways, such as the loss of anti-apoptotic regulators like ARC and promotion of superoxide production. Indeed, the cardioprotective effects of MR antagonists involve the reversal of these non-genomic effects. By stabilizing the oxidant stress it was determined that these non-genomic effects accounted for ~50% of the protective effect in the presence of MR antagonists. Collectively these data suggest that MR activation promotes myocardial damage during reperfusion injury through non-genomic mechanisms and altered transcription.

Biography

Anthony W. Ashton has completed his Ph.D. in 1998 at the University of New South Wales, Australia. His Postdoctoral studies at the Albert Einstein College of Medicine focused on novel mechanisms of treatment for the heart post-infarction. He is currently the Director of Basic Research, in the Division of Perinatal Research at the Kolling Institute for Medical Research in Sydney. He has published more than 51 papers in reputed journals (cited over 1,100 times; h index =23), serves on the editorial board as a reviewer for multiple biomedical journals and for multiple funding bodies.

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