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Novel therapeutic targets and strategies for Myocardial Infarction and Myocardial ischemia-reperfusion injury

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Myocardial infarction (MI) is the major cause of mortality and morbidity due to development of heart failure post-MI throughout the world. MI occurs due to prolonged ischemia resulting from thrombotic occlusion of an atherosclerotic coronary artery. Timely reperfusion with percutaneous transluminal coronary intervention (PCI) or thrombolysis is currently the most effective treatment for MI. However, prompt reestablishment of blood flow by reperfusion therapy can cause complications like reperfusion arrhythmias, micro vascular obstruction and worsening of infarct size. Currently, novel approaches to regenerate damaged cardiomyocyte by stem cell therapy and enhance myocardial repair by promoting angiogenesis in ischemic zone still require optimization for clinical success. In recent years, EphA receptors targeting cell survival pathways, have emerged as potential therapeutic targets for Myocardial infarction. Activation of EphA2 receptors by intramyocardial administration EphrinA1Fc has salvaged ischemic myocardium through anti-apoptotic and anti-inflammatory effects. Further, in silico and cell line studies identified Doxazosin as a novel small molecule agonist for EphA2 receptors. Therapeutic modulation of EphA2 receptor by Doxazosin has recently shown to protect myocardium from reperfusion injury via PI3K/Akt/eNOS signalling pathway. In the recent years, 'Ischemic postconditioning (IPostC)', comprising of alternate cycles of ischemia and reperfusion of short duration applied after an ischemic event, just at the onset of reperfusion, represents a promising strategy against reperfusion injury. Initial studies in small number of patients performed by direct stenting illustrated reduction in infarct size, however, no reduction was reported by studies employing thrombus aspiration/thrombectomy including the largest clinical trial DANAMI-iPOST. However, considering the delayed benefits of IPostC in a subgroup of DANAMI3-iPOST patients without thrombectomy, like improved ejection fraction after 3-15 months and reduced heart failure, a clinical trial iPOST2 (2019 – 2033) is investigating the effect of IPostC without thrombectomy on clinical outcomes in STEMI patients.

Conclusion: EphA2 receptors can be explored by future studies for treatment of MI and prevention of reperfusion injury.

Speaker Biography

Kamaldeep Kaur has her expertise in Cardiovascular, Diabetes and diabetic vascular complications and Parkinson disease research. She has completed research work of M. Pharm. Thesis project under guidance of Dr. Manjeet Singh (guide) and Dr. Nirmal Singh (co-guide) titled: "Implication of PKC-δ isoform in myocardial ischemia reperfusion injury' from Punjabi University, Patiala and PhD. Thesis research work under guidance of Dr. Nirmal Singh titled " Studies on novel targets in Postconditioning to attenuate ischemia and reperfusion injury" exploring the role of DDAH/ADMA/eNOS/NO pathway and EphA2 receptors as novel targets in postconditioning. She has guided Research projects of 9 M. Pharm. Students. Her lab is investigating novel targets in ischemic postconditioning, pharmacological postconditioning, and remote ischemic preconditioning to attenuate myocardial ischemia reperfusion injury. Currently, in her lab novel targets are being investigated for Diabetes Mellitus. In future, drugs targeting Diabetic vascular complications will be investigated through blood flow monitoring or imaging.

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