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RESEARCH ARTICLE

A review on Late phase ischemic preconditioning.

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Abstract

Ischemic preconditioning consists of brief episode of sub lethal ischemia followed by reperfusion. It is a biphasic phenomenon, which starts within minutes and get wanes off gradually within 2 to 3 hours and also called as classical preconditioning and the other phase which appear after 12-24 hours called as late phase of ischemic preconditioning (or delayed phase) which lasts up to 3 to 4 days also called as second widow of protection. Unlike the early phase of ischemic preconditioning, the late phase of ischemic preconditioning protects not only against the myocardial infarction but also include protection against myocardial stunning. Both these phases, early and delayed are responsible for the protection against myocardial infarction and myocardial stunning.

Late phase of ischemic preconditioning involves certain mechanisms that includes first one as those species which are generated during the starting ischemic insult and responsible for the activation of late preconditioning triggers. Second mechanism includes those which are activated after 24- 72 hours of the ischemic insult and responsible for the activation of mediators of late preconditioning. The third one is activated by the action of triggers to show the actions of mediators. All these mechanism are in sequences, former is upstream signal for the next one and they were activated only after preconditioning stimulus. This phenomenon of ischemic preconditioning shows its beneficial effect via involvement of certian triggers and meditors like COX-2, NO, Aldose reductase, etc.

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The heart posses a notable capability to adapt stress by changing its phenotype which makes it more resistant to the injury and this remarkable ability is illustrated by the phenomenon of preconditioning (PC), it is the process whereby the tolerance of the myocardium is enhanced by the sublethal ischemic stress. Ischemic preconditioning is a effective strategy against heart from ischemia reperfusion injury (Murray et al. 1997). Ischemic preconditioning consists of brief episode of sub lethal ischemia followed by reperfusion (Tomai et al., 1999). It is a biphasic phenomenon, which starts within minutes and get wanes off gradually within 2 to 3 hours and also called as classical preconditioning (Downey and Cohen, 1997, Yellon and Downey, 2003) and the other phase which appear after 12-24 hours called as late phase of ischemic preconditioning (or delayed phase) which lasts up to 3 to 4 days also called as second widow of protection. Unlike the early phase of ischemic preconditioning, the late phase of ischemic preconditioning protects not only against the myocardial infarction but also include protection against myocardial stunning. Both these phases, early and delayed are responsible for the protection against myocardial infarction and myocardial stunning. Classical preconditioning include four 5 min- periods of coronary occlusion, interspersed with 5 min reperfusion before a global ischemia of 40 minutes occlusion of the same coronary artery (Marber et al., 1993).

There are various non pharmacological and pharmacological stimuli of delayed preconditioning which are responsible for the delayed protection against myocardial ischemia/ reperfusion injury. The former one include heat stress (Currie et al., 1988), rapid ventricular pacing (Kaszala et al., 1996) and exercise (Yamashita et al., 1999). The later one include naturally occurring and often noxious agents such as endotoxin (Brown *et al.*, 1989), tumour necrosis factor- α [TNF- α] (Brown *et al.*, 1989), TNF- β , interleukin-1 (Nelson *et al.*, 1995), and drugs used for clinical purpose such as adenosine receptor agonists (Baxter *et al.*, 1994), NO releasing agents (Takano *et al.*, 1998), endotoxins derivatives like monophosphoryl lipid A [MLA] (Yao *et al.*, 1993) and opioid agonists (Fryer *et al.*, 1999).

Mechanism of late preconditioning:-

Late phase of ischemic preconditioning involves certain mechanisms that includes first one as those species which are generated during the starting ischemic insult and responsible for the activation of late preconditioning triggers (Bolli, 2000). Second mechanism includes those which are activated after 24- 72 hours of the ischemic insult and responsible for the activation of mediators of late preconditioning. The third one is activated by the action of triggers to show the actions of mediators. All these mechanism are in a sequences, former is upstream signal for the next one and they were activated only after preconditioning stimulus (Bolli, 2000).

Initiators of late preconditioning:-

The brief episode of ischemia and reperfusion is responsible for the generation of wide variety of metabolites and ligands. Among these metabolites and ligands it was found that certain chemical signal such as nitric oxide [NO], adenosine, opioid receptor agonist are involve for the initiating the late phase of ischemic preconditioning (Bolli, 2000).

The concept that adenosine is involved in initiating the late preconditioning was first proposed by Baxter (Baxter *et al.*, 1994) However the involvement of adenosine receptor in late preconditioning is under investigation. It was reported in previous studies that 2-chloro-NCPA⁶-cyclopentyladenosine (CCPA) induced preconditioning which is highly selective for A₁ is blocked by A₁ antagonist (Takano *et al.*, 1999). therefore it can be concluded that the agonist elicit delay cardioprotection by A₁ receptor. Recent evidences had also suggested that the selective activation of A₃ receptor is also playing an important role in initiating the delayed protection against infarction. Thus it can be concluded that the pharmacological activation of A₁ and A₃ receptor can elicit late precondition infarction (Bolli, 2000).

It was also demonstrated in various studies that NO is also an important factor that involves in initiating the ischemia induced by late preconditioning against myocardial infarction where exogenous NO can reproduce late preconditioning. It has also been reported that the biosynthesis of NO in myocardium will get enhanced during the brief episodes of ischemia (Qiu *et al.*, 1997). Nitric Oxide (NO) play an important role in IPC and IPOC induced cardioprotection by activating cyclic guanosine monophosphate (cGMP)/ protein kinase G (PKG)- dependent signaling pathway. NO directly modify protein sulfhydryl residues through protein S-nitrosylation (SNO), which has emerged as an important post-tanslational protein modification in cardiovascular signaling and produces cardioprotection (Murphy *et al.*, 2004).

Moreover, it was also found that reactive oxygen species (ROS) also initiate the delayed phase of cardioprotection (Sun et al., 1999). It was supported by the fact that the combination of antioxidants (Superoxide dismutase + catalase + mercaptopionyl glycine) had prevented the development of late preconditioning against stunning (Sun *et al.* 1999). However MPG alone involves in preventing the ischemia induced late preconditioning against infarction (Yamashita *et al.*, 1998), arrhythmias (Yamashita *et al.*, 1998), coronary endothelial injury, heat stress induced (Kaeffer et al., 1997; Yamashita *et al.*, 1998).

Actiavtion of δ_1 - opioid receptors are also involved in inducing a delayed infarct sparing effect after 24- 48 hours (Fryer *et al.*, 1999; Guo *et al.*, 2000).

Effectors of Late phase of Ischemic preconditioning:-

Late phase of preconditioning requires the synthesis of new protein. Several proteins have been proposed as the possible effectors of protection afforded by the late phase of precondition HSP, NOS, COX-2, Aldose reductase, and antioxidant enzymes (Bolli, 2000).

Nitric oxide plays dual role in late preconditioning against stunning acting initially as the triggers and subsequently as the mediator of the protection. Bolli and his coworker has implicated that the synthesis of nitric oxide (NO) is an important mediator of late phase of ischemic preconditioning (Tokano et al., 1997, Guo et al., 1999). There are three isoform of nitric oxide synthase (NOS) found in myocardium i.e. endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS). The activity of first two isoform of nitric oxide synthase are regulated by cytosolic concentration of calcium and by the presence of different co-factors like tetra hydrobiopterin (BH₄), magnesium and NADPH. The activity of third isoform iNOS is calcium independent synthase and shown by protein transcription. The ischemic stress leads to upregulation of transcription factors such as NF- κ B (Brown *et al.*, 1989, Brown *et al.*, 1990) and this protein transcription is responsible for the upregulation of iNOS and therefore responsible for the production of nitric oxide in delayed phase of preconditioning (Bolli, 2000). It has been reported by researchers that iNOS is the specific nitric oxide synthase responsible for the cardioprotective effect of late phase of ischemic preconditioning. (Takano et al., 1998).

The certain pathological conditions like ischemia, hypoxia, and oxidative stress are also responsible for the upregulation of cyclooxygenase-2 enzyme (Shinmura et al., 2000, Bolli et al., 2002). COX-2 protein will get upregulated after the 24 hours of ischaemic pc along with the increased myocardial levels of PGE₂, 6-keto-pgf₁ and 2 α . The necessity of COX-2 activity can be demonstrated by observed destruction of the increased prostanoids and the completely blockade of the cardioprotective effect of late PC after the administration of selective inhibitors of COX 2 (N-398 and celecoxib) after 24 hours of ischaemic preconditioning (Shinmura *et al.*, 2000).

It has been documented that vascular endothelium is major source of COX-2 enzyme (Bryant et al., 1998, Schror, 2009). It was also documented that COX-2 is involve in the cardioprotective effect of late phase of ischemic preconditioning (Yadav et al., 2010). The cardioprotection produces by this enzyme is mediated by prostaglandin receptor i.e. PGI₂ (Shinmura et al., 2002) and also by making a complex with the nitric oxide (NO) (Ajmani et al., 2011).

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Aldose reductase is as an enzyme which catalyzes the metabolism of glucose to sorbitol and also involves in the detoxification of lipid aldehydes derived from the reactive oxygen species (Srivastava *et al.*, 1998). It has been found that the protein expression of aldose reductase will get up regulate after the 24 hours of ischemic pc in conscious rabbit (Shinmura *et al.*, 2000). Thus it can be concluded that aldose reductase must be the third necessary mediator involved in the cardioprotective action of ischemic preconditioning, however the mechanism involved in it is remains unclear.

A study conducted on isolated neonatal myocytes had found that MnSOD an antioxidant enzyme is necessary for ischemia induced late PC. An increased level of MnSOD is observed after the 24 hours of ischaemic pc due to the production of ROS, TNF- α and interleukin - 1 β . MnSOD induction is responsible for the increasing the Late phase of Ishcemic preconditioning beneficial activity after the heat stress, exercise. The activity was seen to be increased by increasing the MnSOD due to the involvement of ROS, TNF- α and interlukin- 1 β (Guo *et al.*, 2000; Yamashita *et al.*, 1999 ; Yamashita *et al.*, 2000)

In the previous studies it has been reported that over expression of Heat shock protein (HSP) 70 in transgenic mice shows protection against ischemia/reperfusion injury. But, it was also in controversial that whether the pharmacological preconditioning or ischemic preconditioning up regulate the HSP-27 in-vivo. Since the HSP-27 is a substrate for the p38 nitrogen activated protein kinase pathway, which is activated after 24 hours of CCPA administration. Hence the HSP-27 is responsible for the post transitional modulation which play an important role in mediating the delayed cardioprotection is afforded by CCPA (Dana *et al.*, 2000).

Conclusion:-

It was concluded that the pharmacological and cardioprotective activity of Late phase of ischemic preconditioning is due to involvement of certain initiators and mediators. The triggers of late phase of ischemic preconditioning includes Adenosine receptors including A1 and A3, Nitric oxide involving three nitric oxide synthase i.e. eNOS,

iNOS, and nNOS, Reactive oxygen species, and some opioids receptors like δ_1 opioid receptor. They all were responsible for triggering the late phase of ischemic preconditioning.

There are certain mediators which is responsible for the cardioprotective effect including NOS, cyclooxygenase-2 (COX-2), aldose reductase, antioxidants enzymes, and heat stress proteins.

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