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Review

Is oxytocin a therapeutic factor for ischemic heart disease?

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ABSTRACT

Ischemic heart disease (IHD) is among the most important and top ranked causes of death in the world, and its preventive and interventional mechanisms are actively being investigated. Preconditioning may still be beneficial in some situations such as IHD. Development of cardioprotective agents to improve myocardial function, to decrease the incidence of arrhythmias, to delay the onset of necrosis, and to limit the total extent of infarction during IHD is of great clinical importance. In order to reduce morbidity, a new treatment modality must be developed, and oxytocin may indeed be one of the candidates. There is increasing experimental evidence indicating that oxytocin may have cardioprotective effects either by decreasing the extent of reperfusion injury or by pharmacologic preconditioning activity. This review shows that in the presence of oxytocin, the cardioprotective effects may be increased to some extent. The presented board of evidence focuses on the valuable effects of oxytocin on myocardial function and candidates it for future clinical studies in the realm of ischemic heart diseases.

Contents

1. Introduction

Ischemic heart disease (IHD) is among the most important and top ranked causes of death in the world, and its preventive and interventional mechanisms are actively being investigated. Despite the IHD optimal therapies, the rate of morbidity and mortality are still high, with exceeding financial impact [17]. Thus, development of novel cardioprotective strategies continues to be felt.

Ischemia, restriction of coronary blood supply and consequent loss of oxygen rapidly stop mitochondrial oxidative phosphorylation [74]. Diminished energy production causes progressive depletion of cellular ATP stores and creatine phosphate. Anaerobic glycolysis and lactate accumulation lead to cellular acidosis [74,100]. Subsequently, contractile function and membrane ATP-dependent ion transport are impaired [74]. Cellular acidosis further stimulates Na^+–H^+ and Na^+–Ca^{2+} exchangers, resulting in an

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increase in cytosolic Na^+ and Ca^{2+} followed by intracellular K^+ loss. These changes shift the membrane resting potential to the higher depolarizing values and prolong action potential duration. As such, the cytosol is overloaded with Ca^{2+} that overflows into the mitochondrial matrix [76,100]. Calcium flux across the inner mitochondrial membrane regulates cell energy production and activates cell-death pathways.

Based on the researches in the recent decade, reperfusion or re-establishing blood flow into the ischemic myocardium can limit the infarction size and reduce untoward sequels. However, reperfusion itself causes striking damages in comparison with ischemia alone [100]. Oxygen radicals, calcium ions, neutrophils, and reactive oxygen species (ROS) are known mediators of reperfusion injury [74]. These changes are accompanied by accumulation of catabolites and by products, osmotic load, ROS production, and Ca^{2+} sensitive enzymes activation. These responses create cytoskeletal damage and membrane phospholipids imbalance. Severe membrane damage, due to loss of phospholipids, lipid peroxidation, and cytoskeletal disruption are mediators of irreversible stage of injury [100]. Although re-oxygenation and ATP regeneration concomitantly happen during reperfusion, electron transport chain damage results from increased mitochondrial ROS production. Increased mitochondrial ROS and Ca^{2+} load lead to mitochondrial permeability transition pore (mPTP) opening followed by cellular ATP loss. ATP reduction and ion homeostasis deregulation result in massive cell swelling, plasma membrane disruption, and cell death [76]. Modification of the cellular events during ischemia–reperfusion (I/R) is the main goal of pharmacotherapy and other therapeutic measures [45]. Cardioprotective interventions originally affect the mitochondria and reduce cell death [76]. Preconditioning comprises cardioprotective signaling pathways end which with decreased Ca^2 and ROS load, increased G-protein-coupled receptor, protein kinases and mitochondrial ATP-dependent potassium (mitoKATP) channel activities, and decremented apoptotic signaling and mPTP opening [47]. Therefore, therapeutic strategies to protect the ischemic myocardium have been studied extensively. Development of cardioprotective agents in order to improve myocardial function, decrease the incidence of arrhythmias, delay the onset of necrosis, and limit the total extent of infarction during I/R is of great clinical importance.

2. Preconditioning

Despite impressive developments in therapeutic techniques of ischemic heart diseases, subsequent injuries remain the head of mortality and morbidity [36]. Investigators have devoted high attention to protect the ischemic tissue with the purpose of cell necrosis and apoptosis prevention and maintain organ natural function [100]. Cardiac preconditioning represents a potent and reproducible method to render the myocardium more resistant against irreversible structural and functional damage induced by a variety of deleterious stimuli [32,100]. Preconditioning that was first described in the canine myocardium by Murry et al. [77] remained the gold standard in all investigational cardioprotective measures. There are three different forms of preconditioning. First, the ischemic preconditioning (IPC) which is related to repeated subjecting tissues to brief episodes of ischemia or hypoxia. In IPC, the heart is exposed to episodes of 5 min ischemia via the circumflex coronary artery ligation, followed by 5 min reperfusion just before a prolonged ischemia phase. This technique protects tissues against sustained I/R harmful effects [100]. Another form of preconditioning is known as “remote preconditioning” or ischemic preconditioning at a distance, which can afford myocardial protection probably via neural and/or hormonal activation of conditioned organs. Studies have focused to find an agent suitable for myocardial cells protection against injurious effects of I/R [36]. Study of IPC mechanisms led us to this conclusion that various pharmacological modalities may mimic preconditioning-like effects in experimental animals. Pharmacological preconditioning (PPC) can afford safer and less invasive approaches than IPC for stimulating cardioprotection in humans [100]. Furthermore, many of preconditioning agents are classified in this category. Studies have recently shown that hormonal compounds such as oxytocin (OT) represent potential cardioprotective properties. One of the major goals of cardiovascular researches is to identify a reliable cardioprotection intervention that can salvage ischemic myocardium. Prior pharmacological agents used in I/R injuries had limited investigational values or failed to furnish useful clinical treatments. In this regard, OT can be considered as a pharmacological preconditioning agent that represents a novel cardioprotective strategy in the setting of elective myocardial ischemia.

3. Oxytocin

In 1906, Sir Henry Dale discovered a nine amino acid neuropeptide named oxytocin [22]. It was the first peptide hormone structurally assessed and chemically synthesized in biologically active form by Vincent du Vigneaud and brought him the Nobel Prize in 1955 [25]. OT is primarily released from the posterior pituitary gland in response to various physiological stimuli and plays dual role as a neurotransmitter/neuromodulator and a hormone. It primarily acts on uterine mediating the forceful contraction during parturition and causes milk ejection in lactational period. Since OT is found in plasma and neurohypophysis of both sexes in equivalent concentrations, it should have a wide-spectral physiological activity [38]. The heart, especially the right atrium is also one of the sources of high OT content [38,41]. OT receptors have been identified in the peripheral tissues including the kidney, heart, thymus, pancreas, and adipocytes [38]. Its receptor is a G protein coupled that produces IP3 and DAG via phospholipase C activation. IP3 in turn releases Ca^{2+} from intracellular sources and activates protein kinase C (Fig. 1). Protein kinase C itself phosphorylates target proteins and initiates variety of cellular events [38]. OT is pleiotropic hormone acting on classical endocrine, paracrine and autocrine fashion [38]. It regulates basic cardiovascular function, for instance, cardiomyocytes survival, tissue regeneration [59], stem cell differentiation [73,86], hypertrophy and glucose uptake potentiation, negative inotrophic and chronotrophic effects [31,82], anti-inflammatory and pro-inflammatory cytokines balance [51], hydromineral balance by ANP release [87], vasodilatation and endothelial cell growth via NO pathway [23,67], electrical activity control and vascular reactivity [21,53]. Few studies are available to support the therapeutic use of OT in cardiovascular diseases. Pharmacological interventions have also led to improved survival of patients with IHD, though they may fail to restore dead myocardium. The ultimate goals are myocardial regeneration leading to clinical improvement with no cruel unfavorable properties.

4. Oxytocin and tissue protection

Numerous studies reported OT’s protective effects against I/R-induced tissue injury [1,2,82]. OT’s tissue protective properties were assessed in rat’s sepsis-related organ damage [50]. Its anti-inflammatory effects prevent epithelial damage and inflammatory cell infiltration in colon and uterus [50]. OT’s renal protective roles against I/R-induced oxidative damage are also mediated via inhibition of neutrophil infiltration, ROS release and inflammatory cytokines [9]. It also provides hepatic support against I/R injury which is related to its inhibitory effects on neutrophil infiltration and nitric oxide (NO) production [27,28]. OT cardioprotective