How does Viagra protect the ischemic heart?

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SILDENAFIL, better known as Viagra, is the first oral medicine approved for treating erectile dysfunction. Interestingly, sildenafil was originally intended for coronary heart disease. But the initial result from the clinical study on its effectiveness easing coronary syndrome was gloomy. On the other hand, patients reported a side effect: sildenafil may enhance erectile function. This side effect quickly took the place of its primary application, and sildenafil grew to be a multibillion dollar blockbuster in the drug market. However, the story does not just end there. New excitement and surprises keep emerging from the study on sildenafil. Over the past few years, sildenafil was found to protect hearts against ischemia-reperfusion injury (3, 8). Studies also showed that sildenafil suppresses cardiac hypertrophy and improves heart function in mice exposed to chronic pressure overload (9). Although a variety of mechanisms have been implicated in the effect of sildenafil, the signaling process that mediates the cardioprotection of sildenafil in ischemic hearts has not been fully understood. Das et al. (2) provide compelling evidence that ERK1/2 may be the key mediator that bridges cGMP-dependent protein kinase (PKG) to various downstream protective mechanisms in the action of sildenafil.

Sildenafil is a specific inhibitor of phosphodiesterase-5 (PDE-5), an enzyme responsible for breaking down cGMP. By inhibiting PDE-5, sildenafil raises cytosolic cGMP concentrations leading to PKG activation. Since Kukreja and colleagues (8) first reported that sildenafil protected hearts against ischemic injury in a rabbit ischemia-reperfusion model, the beneficial effect of sildenafil on ischemic hearts has been confirmed by other groups on different animal species. Sildenafil induces both acute and delayed protection to the hearts subjected to ischemia and reperfusion. A number of mechanisms have been reported to account for the effect of sildenafil on ischemic hearts. These include upregulated endothelial nitric oxide synthase/inducible nitric oxide synthase (eNOS/iNOS, respectively) expressions, PKC activation, induction of antiapoptotic protein Bcl-2, opening of mitochondrial ATP-sensitive K+ channels (KATP), etc. In an earlier study published by the same group, Das et al. (3) used pharmacological as well as gene knockdown approaches confirming that PKG activation was necessary for the cardioprotective effects of sildenafil. However, an important question remains regarding how PKG activation is linked to other downstream protective mechanisms. These authors previously found that sildenafil induced ERK1/2 activation in a PKG-dependent manner (3). ERK1/2 belongs to a family of MAPKs, which have been shown to play crucial roles in cell survival and ischemic preconditioning. Thus ERK1/2 appears to be an ideal candidate to transmit the signal of PKG activation to other pathways in sildenafil-treated hearts.

Indeed, Das et al. (2) showed that inhibiting ERK1/2 with PD98059 eradicated both acute and delayed protective effects of sildenafil on postischemic hearts. It should be mentioned that it is not uncommon that small-molecule kinase inhibitors exhibit off-target effects. But PD98059 has been extensively scrutinized and found to be rather selective to MAPK kinase 1, the upstream kinase of ERK1/2 (4). Further studies revealed that the sildenafil-elicited protective events such as eNOS/iNOS and Bcl-2 upregulation can all be blocked by PD98059. On the other hand, PD98059 had no effect on the PKG activation in sildenafil-treated hearts. These findings establish ERK1/2 as a key mediator that relays the signal of sildenafil-induced PKG activation to other downstream pathways.

Das et al. (2) have compiled a schematic diagram to depict the signaling transduction process underlying the protective effect of sildenafil on ischemic hearts. Although this scheme is certainly subject to constant modification, it does point out many directions of future research. For example, how does PKG activate ERK1/2? Is this a direct effect or a process involving other mediators? How does ERK1/2 activation enhance iNOS and eNOS expressions? iNOS expression is known to be primarily governed by NK-κB and signal transducer and activators of transcription 1 (STAT1). Although many studies have shown that ERK1/2 may mediate cytokine-induced STAT1 activation, whether ERK1/2 initiates iNOS gene expressions via STAT1 still needs to be examined in the context of sildenafil-treated hearts. There are studies showing that in lysophosphatidylcholine-treated endothelial cells, ERK1/2 activation may stimulate the binding of Sp1 to the eNOS promoter, leading to increased eNOS expressions (1). Whether Sp1 is involved in eNOS upregulation in hearts after sildenafil treatment is an interesting question for future investigation. Furthermore, the proposed mechanism may provide a plausible explanation for the delayed cardioprotection. On the other hand, the acute cardioprotection of sildenafil is clearly unrelated to the increases in eNOS/iNOS expression. Further studies are needed to elucidate how sildenafil-induced ERK1/2 activation leads to cardioprotection in the acute setting.

Another intriguing finding from this study is that a single injection of sildenafil resulted in prolonged inhibition of GSK-3β. ERK1/2 inhibition significantly reversed sildenafil-induced GSK-3β inhibition. Das et al. (2) speculate that GSK-3β inhibition may be involved in the delayed cardioprotection by sildenafil. Indeed, the inactivation of GSK-3β has been proposed as a common target of various protective signals in ischemia-initiated preconditioning (6), but how GSK-3β inhibition induces protection to ischemic hearts remains incompletely understood. The mitochondrial permeability transition pore (mPTP) has been reported to be the target of GSK-3β. GSK-3β inhibition reduces mPTP openings, and this gives rise to cell protection. In addition, recent studies demonstrated that GSK-3β profoundly regulates progenitor cell proliferation. In fact, small molecule GSK-3 inhibitors have been used to...
maintain the pluripotency of stem cells (5). Numerous studies have reported that progenitor cell infusions protect the heart from ischemic injury. We can hypothesize that sildenafil-induced GSK-3/β inhibition may promote progenitor cell proliferation. It will be of significant interest to investigate whether sildenafil affects progenitor cell proliferation, and if so, how this is related to its delayed cardioprotective effect.

It appears that after the unintended effect of sildenafil took over the center stage of its application for so many years, the originally sought cardiovascular benefit may eventually materialize. It is noteworthy that the doses of sildenafil used in the cardioprotection study are comparable to those for treating erectile dysfunction (2). Since sildenafil has been widely prescribed for over a decade, a retrospective clinical study on the effect of sildenafil on myocardial infarction is warranted. In fact, there was a study reporting that the incidence of myocardial infarction was seemingly lower among the sildenafil users (7). Certainly, these results need to be further verified. The study by Das et al. (2) was conducted on male mice. It remains to be seen whether female animals can similarly benefit from sildenafil against ischemia-reperfusion injury. Unfortunately, retrospective studies will unlikely provide an answer to this question since female sildenafil users are scarce. Thus a carefully controlled clinical trial on the effect of sildenafil on patients, both men and women, with ischemic heart disease deserves priority.

GRANTS

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REFERENCES