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Review on Nitric Oxide, Carbon Monoxide and Antisense Based Therapy towards Treatment of Restenosis

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Abstract

Balloon angioplasty has shown tremendous improvement in the treatment of atherosclerosis, but arterial renarrowing (restenosis) exists despite the benefits of intravascular devices called stents. Nitric Oxide (NO), carbon monoxide (CO) and Antisense therapy is some of the new potential treatment modalities. NO deficiency is associated with several vascular occlusive diseases, since NO regulates diverse aspects of blood vessel functions. More restricted human studies and several preclinical studies suggest that, NO supplement may solve the restenosis problem, although the data do not conclusively demonstrate this effect. CO, similar to NO, inhibits vascular smooth muscle cells (VSCM) proliferation and in turn relaxes blood vessels and inhibits platelet aggregation. Thus it is recently suggested that inhaling CO could address the restenosis problem. Recent advances in vascular gene transfer have shown positive results for cardiovascular diseases, particularly in the treatment of restenosis. Uncoiling the DNA, transcription of DNA, export of RNA, DNA splicing, RNA stability or RNA transcription involved in the synthesis of proteins in cellular proliferation are some of the process involving antisense based approach. This review focuses on discussing the recent advancements in the treatment of restenosis.

Keywords: Restenosis; Nitric oxide; Carbon monoxide; Antisense; Angioplasty

Introduction

Report form American Heart Association that is published in 2014 highlights the unremitting predominance of cardiovascular disease (CVD) as a cause of morbidity and mortality [1,2]. One-third of the global mortality and the leading cause of death in the US and Europe is attributed to cardiovascular maladies. In US alone, more than half of all cardiovascular events in men and women under age of 75 reflect ischemic coronary heart diseases, which are elicited by coronary artery in which the lumen is narrowed by advanced atherosclerosis. A major breakthrough in cardiovascular therapy was established in 1977, when the first percutaneous transluminal coronary angioplasty (PTCA) by using an inflatable balloon catheter to dilate an obstructed coronary segment. A surgical or non-surgical procedure to remove the blockade may fail as a result of several unfavorable combinations, which can increase the likelihood of an adverse event or death. Indeed, 40% of the cases that received PCTA experienced recurrent myocardial ischemia, due to re narrowing of the treated artery within 6 months.

Arterial injury response to neointimal hyperplasia

Neointimal hyperplasia (NH) is an exaggerated healing process that occurs in the vessel wall after injury. NH is responsible for restenosis, limiting the success of many cardiovascular procedures. The development of NH is a complex process initiated by injury and exposure to the vascular smooth muscle cells (VSMC) to circulating blood elements. The process is further explained in the following steps (Figure 1) (Table 1).

Despite having the success of treating coronary heart diseases by angioplasty, still there is tremendous need for addressing restenosis [3-8]. Several pharmaceutical approaches including delivery of anti-hypertensive agents, calcium channel blockers, lipid-lowering drugs and antioxidants have shown limited success in treating restenosis [5,6,9,10]. Best and most acceptable way to reduce restenosis rate in the clinic is with stents, by providing a larger initial lumen diameter, covering vessel dissections and supporting the expanded artery with sufficient rigidity [11,12]. Although there is some success with restenosis problem by utilizing stent based approach, there is still a need for anti restenotic drug-based therapy. In the quest for this process, several therapies were studied and discussed in the following sections.

Nitric oxide based therapy in treating/preventing restenosis

Several research groups have demonstrated the role of nitric oxide (NO) in the regulation of neointimal hyperplasia. Any defect in the pathway of NOS/NO pathway promote abnormal remodeling and neointimal hyperplasia. NO based therapy has shown several mechanisms in regulating the vascular smooth muscle cell (VSCM) proliferation neointimal hyperplasia. Some of the several effects of NO on neointimal hyperplasia include,

i) Inhibition of platelet aggregation and adhesion

ii) Inhibition of leukocyte chemotaxis

iii) Inhibition of vascular smooth muscle cell proliferation and migration

iv) Stimulation of VSMC apoptosis

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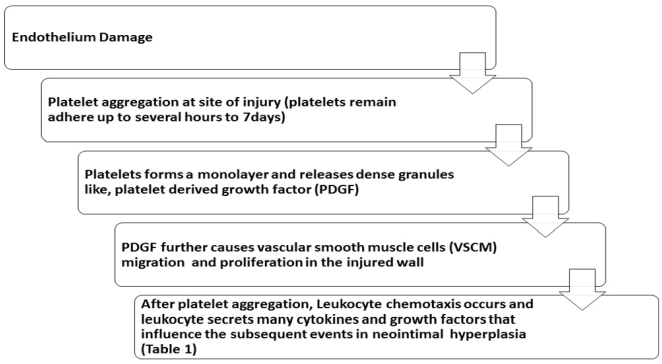

Figure 1: Step by step process depicting the pathogensis of neointimal hyperplasia.

	Cell Source		
Growth Factors, Cytokines	Leukocytes	Monocytes, macrophages	Mast Cells
IGF-I		X	
PDGF		X	X
TGF-α		X	
TGF-β	X	X	X
VEGF	X	X	X
EGF		X	
FGF		X	
TNF-α	X	X	X
IL-Iβ	X	X	X
IL-4	X		X
IL-6		X	X
IL-8	X	X	X
IL-10		X	X
IL-18	X	X	X
MCP	X	X	X

Table 1: Cellular sources of growth factors and cytokines involved in the pathogenesis of fibroproliferative vasculopathies. Adapted from Mirtra el al. [2].

v) Stimulation of endothelial cell proliferation

vi) Inhibition of endothelial cell apoptosis

Given the role of NO in maintaining a normal vascular environment, many research groups have studied the effect of replacement of NO at the site of injury would prevent development of neointimal hyperplasia. Sadaf and co-workers have attempted to summarize the NO-based therapies that have been investigated and presented in the form of a table [13].

Inhalation of nitric oxide

Lee and co-workers have studied the effect of inhalation of nitric oxide (NO) on neointimal hyperplasia after balloon injury of the rat carotid artery. The results from the studies confirmed that, there was a 43% reduction in the Intima-Media (I/M) area ratio in rats. Inhalation on NO for the period of 2 weeks have shown the reduction in I/M area, whereas treating the injured artery for 1 week showed no difference in the I/M area ratio. But in contrast, studies by Rich et al. demonstrated that the levels of NO were undetectable in the artery of isolated perfused rat lungs ventilated with NO [14].

Administration of nitric oxide donors systemically

NO precursor, L-arginine was administered to the rabbits after balloon angioplasty to thoracic aorta by Mc Namara and co-workers [15]. L-arginine was administered from 2 days before to 2 weeks after angioplasty and the results showed that there was ~ 39% decrease in neointimal hyperplasia compared to control. To further confirm the effect of NO as therapeutic agent in decreasing the neointimal hyperplasia, NO inhibitor L-NAME was co-administered with L-arginine reduced the effect in decreasing the neointimal hyperplasia. In another study by Chen et al administration of L-arginine (2.5 mg/mL) in drinking water of rats reduced the I/M area ratio by 65% and 26% reduction in the intimal cell proliferation compared to controls [16-18]. Despite the success in animal models, no human trials have demonstrated the clinical efficacy of systemic L-arginine administration.

Groves and co-workers have studied the effect of systemic administration of No donor molsidomine every 8 h for 48 h in porcine carotid balloon angioplasty and the results showed 32% reduction in neointimal hyperplasia at 21 days. However, the effect was observed only when the internal elastic lamina remained intact after angioplasty. Unfortunately, administration of systemic NO has not consistently demonstrated inhibition of neointimal hyperplasia in human subjects. In another study, Angioplastic, Coronaire, Corvasal, Diltiazem study showed that patients receiving NO from intravenous linsidomine, followed by oral molsidomine for a total of 6 months, had a significant improvement with a 10% reduction in lumen diameter [19]. In addition to the conflicting results in human clinical studies; vasodilatation, hypotension, headaches and increased bleeding complications limited its clinical applications.

Nitric oxide synthase gene therapy

Development in the field of gene transfer techniques has major impact in treating vascular disease; especially much effort has been invested in studying the effects of NOS gene transfer to treat neointimal hyperplasia. Sendai virus was first investigated by vonder Leyen to transfer eNOS to rat carotid arteries after balloon angioplasty [20]. The results from the studies demonstrated ~ 70% reduction in neointimal hyperplasia were observed at the end of 2 weeks. Similarly, Chen and co-workers used retrovirus to transfect VSCM with eNOS and the results concluded ~ 37% reduction in neointimal hyperplasia at 2 weeks after injury. Gene transfer of inducible NOS (iNOS) has demonstrated similar effects on neointimal hyperplasia. Adenoviral delivery of human iNOS to rat carotid artery resulted in 95% reduction in intimal thickening at 2 weeks [21].

Local delivery of nitric oxide donors

Many investigators have studied the release of NO locally at the site of arterial injury. Biocompatibility is the primary issue to be focused during the selection of polymer containing NO-donating groups, because polymer induced inflammation has been reported by several research groups [15,22]. A combination of polymers could theoretically offer a more versatile release profile, but such complex coating would likely to cause biocompatibility issues. Several research groups have studied and reported use of NO-releasing polymers locally. Marks and co-workers investigated the effect of polythiolated bovine serum albumin modified to carry several S-nitrosothiol groups, on arterial balloon injury in rabbits [23]. Results from the studies showed that, development of neointimal hyperplasia reduced by ~ 77% when compared to control. Similar results were obtained when vein grafts

treated with L-arginine increased NO levels and reduce neointimal hyperplasia in rabbit vein graft model.

NO-releasing prosthetic materials

Despite the advantages of several therapies mentioned to deliver NO in treating neointimal hyperplasia, there exist some clinical limitations because of systemic side effects, biocompatibility issues, complicated delivery schemes, or inability to delivery NO at the site for prolong period of time. To overcome these problems, recent research has focused on delivering NO through NO-releasing prosthetic materials. Yoon and co-workers utilized NO donor sodium nitroprusside to incorporate into a metallic stent coated with polyurethane polymer to investigate the effect on neointimal hyperplasia [24]. The stented arteries showed increased release of NO and also showed increased local cGMP levels, but failed to show the difference in the neointimal area compared to control. Later, two research groups Hou et al. and Do et al. demonstrated a reduction in neointimal area with NO-eluting stent [25-27]. Hou and co-workers have demonstrated the use of silicone containing sodium nitroprusside to coat the interior of a self-expanding polytetrafluoreethylene stent. From the studies it was found that, the mean neointimal area was reduced from 2.4 mm^2 for control stents to 0.49 mm^2 for NO-eluting stets, which corresponds to 24% reduction of angiographic vessel narrowing.

Recently, prosthetic bypass grafts are modified with NO-releasing molecules and utilized for delivering NO. Research in this field is focusing mainly on the biomechanics of NO release and the effect of these alterations on the prosthetic materials. Smith et al were the first to study the effect of diazeniumdiolated polymers incorporation in vein grafts [28,29]. The results showed that, NO release was achieved immediately, but the long-term biocompatibility limited its potential application. Later, Zhang and co-workers incorporated diazeniumdiolated silica nanoparticles into vascular grafts by embedding them into hydrophobic matrices in the rabbit model [30]. Unfortunately, the vascular grafts showed leaching and measurable levels of carcinogens (nitrosamines) were formed. Therefore, the investigators have attempted to coat grafts with layers of polyvinyl chloride or covalently binding diazeniumdiolates into a polyurethane backbone to prevent leaching of the NO-releasing prosthetic materials.

The main consideration in choosing NO based therapy is due to its antithrombotic, anti-proliferative, anti-inflammatory and vasorelaxant activity. Also, NO insufficiency is a crucial contributor to many occlusive vascular diseases. Human clinical trial data are limited, and conclusively demonstrates that NO based therapy can prevent restenosis in humans is currently lacking [31,32]. Nonetheless, when NO-donors administered systemically, they are prone to express eNOS which may inhibit angiographic restenosis in some clinical studies involving coronary heart disease patients [33]. Therefore, NO based therapies have potential inhibitory role in the development of neointimal hyperplasia.

Carbon monoxide based therapy

Some recent studies demonstrated that heme oxygenase-1-endogenous carbon monoxide-cycle guanosine monophosphate cell signaling system involve in many pathogphsiological processes and the regulation of cardiovascular system. Heme oxygenase-1 (HO-1), the cytoprotective enzyme responsible for the generation of endogenous CO, was shown to regulate endothelial cell proliferation *in vitro* [34]. However, the role and the mechanism of action of HO-1 and CO in endothelial cell repair after trauma have not been evaluated. CO, like the other similar diatomic gas NO, inhibits VSMCs proliferation by activating soluble guanylate cyclase and elevating intracellular sGMP levels. This in turn relaxes blood vessels and inhibits platelet aggregation. Recently it is suggested that endogenous CO play an important role in regulating vascular tone under both physiological and pathological conditions.

The fact that NO promotes the proliferation of endothelial cells and mobilization of endothelial progenitor cells prompted several research groups to investigate the hypothesis that endothelial eNOS may play a role in the effects of CO on endothelial cells [35-38]. Otterbein and co-workers have demonstrated that a 1-hour exposure to CO at low, nontoxic concentrations before injury, with no further treatment, prevented the development of intimal hyperplasia caused by balloon angioplasty via direct effects on VSMC proliferation [39]. In another study by Wegiel and co-workers, they demonstrated the effects of both CO and a CO-releasing molecule (CORM) on the augmentation of endothelial cell proliferation and migration to the injured site in rodent models. Authors conclude from the data that, one mechanism by which CO might promote cell growth is through phosphorylation of eNOS and activation of protein kinase B and retinoblastoma. The ability of CO to increase eNOS phosphorylation, however, may occur indirectly through an upstream potassium channel-mediated event. The results from their study concluded that, CO accelerates reendothelialization of the injured vessel and reported eNOS and NO as essential source for the CO effect. Despite the potential application of CO in treating restenosis, the safety and tolerability in human subjects still needs to be evaluated [40,41].

Antisense

Antisense approach refers to the use of synthetic oligonucleotides or RNA transcripts, which are designed to interrupt synthesis of specific proteins. The antisense approach to inhibit gene expression involves, introducing oligonucleotides complementary to mRNA into cells in order to block any one of the following processes: uncoiling of DNA, mRNA transport from the nucleus to the cytoplasam, intracellular sequestration of the molecule, RNA stability, ribosome assembly, or RNA translation involved in the synthesis of proteins in cellular proliferation [42-48].

One of the potential clinical applications of antisense therapy is the prevention or treatment of restenosis following coronary interventions. The clinical applicability of antisense technology, remains limited due to relative lack of specificity, slow uptake across the cell membrane and rapid intracellular degradation of the oligonucleotides.

A number of animal models include, injured rat carotid model, porcine coronary angioplasty, have been used to demonstrate the effect of antisense oligonucleotides on restenosis. However, unlike human coronaries, rat carotid is completely dependent on SMC migration from the median [49]. Whereas, porcine coronary angioplasty model was comparatively expensive.

Several steps are generally required to document the biological effect of antisense oligonucleotides therapy includes:

i) Target gene mRNA or protein levels should be determined in both treated and control groups.

ii) Further, biological function of the gene should be assessed to demonstrate the activity.

iii) Finally, a specific biological effect should be demonstrated.

Despite the apparent success of antisense oligonucleotides therapy, there exist several limitations for this technology. The oligonucleotides must effectively cross the cell membrane to reach nucleus and must be resistant to degradation. Affinity and specificity towards the target gene is another potential aspect, which needs to be further studied [50]. Due to the strong negative charge present on the surface of the oligonucleotides, prevents them from passing the cell surface passively. However, uptake of oligonucleotides is determined by various factors include, length of the oligonucleotides, total charge of the molecule, lipid solubility and nucleotide concentration [51,52].

Earlier attempts to deliver oligonucleotides to treat/prevent restenosis are by surgical application. The initial clinically applicable devices were catheter-based, which allows the local delivery of oligonucleotides. Phosphorothioate oligonucleotides first utilized the combination strategy of antisense targeting to c-Myc with catheter based delivery to pigs for prevention of restenosis [53]. However, the bolus injection produced a reduction in heart rate, blood pressure and cardiac output in primate models [54,55]. Further development in the field of oligonucleotides delivery includes polymer-coated stents to deliver micromolar concentrations of c-Myc antisense phosphorodiamidate morpholino oligomers (PMO) into vessel walls. Gelatin-coated platinum-iridium stents used to deliver c-Myc antisense oligonucleotides in rabbits have been successfully demonstrated by Zhang and co-workers [56].

The first clinical study demonstrated the safety and feasibility of local delivery of antisense in the treatment and prevention of restenosis. Several studies demonstrated the endoluminal delivery of advanced c-Myc antisense PMO into coronary arteries of rabbit following stent implantation. Kipshidze and co-workers have demonstrated the complete inhibition of c-Myc expression and a significant reduction of the neointimal formation in dose dependent fashion while allowing for complete vascular healing. In another study by same research group, similar results were obtained after implantation of advanced c-Myc antisense PMO eluting phosphorylcholine coated stents in porcine coronary model (Figure 1). Advantage of antisense PMO over other more destructive methods, such as brachytherapy or cytotoxic inhibitors can be accountable to the success of 40% reduction in intima in the absence of endothelial toxicity [57,58].

Conclusion

With increasing trends in the people affected by coronary heart diseases and the advances in technology the treatments for CRD using intervention techniques will increase. The physicians for patients with multivessel disease, diabetes, etc. may also follow intervention treatments. Despite the advantages from intervention therapies there are also limitations like restenosis, which can be solved by using different non-interventional therapies. More research advances addressing the limitations associated with the existing therapies will further benefit the population that is affected by CRD.

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