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Review

Nanoparticle-Mediated Drug Delivery System for Pulmonary Arterial Hypertension

Kazufumi Nakamura [1,*], Hiromi Matsubara [2], Satoshi Akagi [1], Toshihiro Sarashina [1], Kentaro Ejiri [1], Norifumi Kawakita [1], Masashi Yoshida [1], Toru Miyoshi [1], Atsuyuki Watanabe [1], Nobuhiro Nishii [1] and Hiroshi Ito [1]

[1] Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan; akagi-s@cc.okayama-u.ac.jp (S.A.); sarashina.toshihiro@gmail.com (T.S.); eziken82@gmail.com (K.E.); rm3ta6@bma.biglobe.ne.jp (N.K.); masashiyoshid@gmail.com (M.Y.); miyoshit@cc.okayama-u.ac.jp (T.M.); atsunao0422@gmail.com (A.W.); nnnnishii2001@gmail.com (N.N.); itomd@md.okayama-u.ac.jp (H.I.)

[2] Division of Cardiology, National Hospital Organization Okayama Medical Center, Okayama 700-0082, Japan; matsubara.hiromi@gmail.com

* Correspondence: ichibun@cc.okayama-u.ac.jp

Abstract: Nanoparticles have been used as a novel drug delivery system. Drug-incorporated nanoparticles for local delivery might optimize the efficacy and minimize the side effects of drugs. The efficacy and safety of intratracheal administration of prostacyclin analog (beraprost)-incorporated nanoparticles and imatinib, a PDGF-receptor tyrosine kinase inhibitor, -incorporated nanoparticles in Sugen-hypoxia-normoxia or monocrotaline rat models of PAH and in human PAH-pulmonary arterial smooth muscle cells have been reported. The use of inhaled drug-incorporated nanoparticles might be a novel approach for treatment of PAH.

Keywords: pulmonary arterial hypertension; prostacyclin; nanoparticle; drug delivery system

1. Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening and progressive disease characterized by progressively elevated pulmonary vascular resistance (PVR) and pulmonary artery pressure. Increased PVR is induced by pulmonary vasoconstriction, vascular remodeling by intimal and medial hypertrophy, and thrombosis.(1-3) Sustained elevation of pulmonary vascular resistance causes severe right ventricular (RV) hypertrophy and failure, leading to a poor prognosis. PAH-targeted drugs including prostacyclin (prostaglandin I_2), endothelin receptor antagonists (ERAs), phosphodiesterase type-5 inhibitors and a soluble guanylate cyclase stimulator have become available in the past two decades, and treatment with those vasodilators has been effective,(4-8) though PAH is still a fatal disorder in many patients. A new and safe therapy for PAH is therefore needed.

2. Prostacyclin therapy for PAH

The release of endogenous prostacyclin (prostaglandin I_2) is depressed in patients with PAH. Prostacyclin replacement therapy by infusion of epoprostenol sodium, a prostacyclin (prostaglandin I_2), is one of the best treatments available for PAH. Epoprostenol treatment improves symptoms, exercise capacity, and hemodynamics and is the only treatment that has been shown to reduce mortality in patients with idiopathic PAH (IPAH) in randomized clinical trials (RCTs).(6,9) High-dose epoprostenol therapy (>40 ng/kg/min) resulted in marked hemodynamic improvement in patients with IPAH.(4,10) Compared with the baseline state, high-dose epoprostenol therapy reduced mPAP by 30% and PVR by 68%. We have also reported that high-dose epoprostenol has a pro-apoptotic effect on pulmonary artery smooth muscle cells (PASMCs) of patients with PAH via the IP receptor.(11)

However, epoprostenol therapy causes several adverse events and complications such as headache, hypotension and catheter-related infections. Chronic infusion of epoprostenol is performed using a small, portable infusion pump through an indwelling central venous catheter. The most serious complication is catheter-related infections. The catheter infection rate was 0.26 per 1,000 catheter days in PAH patients treated with epoprostenol.(12) Systemic administration of prostacyclin can induce headache, flushing and sometimes severe hypotension at the start of prostacyclin therapy. These problems would be solved if an alternative system to target delivery of the prostacyclin to the pulmonary vasculature without using a central venous catheter is developed.

3. Imatinib for treatment of PAH

Remodeling of the pulmonary artery by an inappropriate increase of PASMCs is problematic in the treatment of PAH. Effective treatment that achieves reverse remodeling is required. This will require anti-proliferative and pro-apoptotic agents for PASMCs.

We have reported that platelet-derived growth factor (PDGF)-BB stimulation caused a higher growth rate of cultured PASMCs from patients with IPAH than that of control cells.(13,14) Imatinib is a drug used to treat certain types of cancer such as chronic myelogenous leukemia and gastrointestinal stromal tumors and a PDGF-receptor tyrosine kinase inhibitor. Schermuly et al reported that imatinib reverses pulmonary vascular remodeling and cor pulmonale in rats with monocrotaline-induced pulmonary hypertension (PH) and in mice with chronic hypoxia-induced PH.(15) Imatinib has anti-proliferative and pro-apoptotic effects on IPAH-PASMCs stimulated with PDGF-BB. (16)

Clinical improvement and hemodynamic improvement have been reported in some patients with PAH who were treated with imatinib.(17,18) However, a randomized, double-blind, placebo-controlled trial showed that imatinib improved exercise capacity and hemodynamics in patients with severe PAH but that serious adverse events and drug discontinuations were common.(19) Since systemic administration of imatinib causes serious adverse events, the development of a new route of administration is required.

4. Nanoparticle-mediated drug delivery system (nano-DDS)

Nanoparticles (NPs) have been used as a novel delivery system for transport of drugs to target organs.(20-22) NPs are taken up by the target organ because of their small size and permeability and their retention effect. Drug release from NPs is controlled according to the NP composition. Thus, drug-incorporated NPs for local delivery might optimize the efficacy and minimize the side effects of drugs.

Liposomes and polymers have been tested nano-DDSs in basic and clinical studies. Liposomes consist of phospholipids that form bilayers with an aqueous phase inside, and are heterogeneous in size, often ranging from a few hundreds to thousands of nanometers in diameter. Two polymers, poly(lactide) (PLA) and poly(lactide-co-glycolide) (PLGA), are used for the synthesis of FDA-approved polymeric biodegradable nano-DDS.(21,23) This type of nanoparticle can be used to achieve the sustained release of encapsulated drug, which takes place concomitantly with the degradation of PLA or PLGA. Various chemicals and nucleotides are incorporated in liposomes and polymers.

As for treatment of PH, treatment with vasodilators such as prostacyclin, ERAs and PDE-5i has been effective,(4-8) though PAH is still a fatal disorder in many patients. A new and safe therapy for PAH is therefore needed. Systemic administration of prostacyclin or imatinb causes several adverse events and complications. Inhaled administration of aerosolized iloprost is also effective, but a high frequency of inhalation of iloprost per day is required. Nano-DDSs for lung would optimize the efficacy and minimize the side effects of drugs. Pitavastatin,(24) nuclear factor kappaB decoy,(25) imatinib,(26) prostacyclin analog,(27,28), fasudil,(29) and antimiRNA-145-incorporated NPs,(30) have been reported to be effective in animal models of PH (Table 1). In this review, we summarize results of recent studies using prostacyclin analog-incorporated NPs (27,28) and imatinib-incorporated NPs.(26)

Table 1. Nanoparticle-mediated drug delivery system for pulmonary arterial hypertension treatment

Drug	Delivery system	Animal model	Route of admin.	Refs
Pitavastatin	Polymer (PLGA)	MCT-induced rat model	Intratracheal	(24)
NF-kB decoy	Polymer (PEG-PLGA)	MCT-induced rat model	Intratracheal	(25)
Imatinib	Polymer (PLGA)	MCT-induced rat model	Intratracheal	(26)
Beraprost	Polymer (PLA and PEG-PLA)	MCT-induced rat model	Intravenous	(27)
Beraprost	Polymer (PLGA)	MCT-induced rat model	Intratracheal	(28)
		Sugen/hypoxia rat model		
Fasudil	Liposome	MCT-induced rat model	Inhalation	(29)
AntimiRNA-145	Liposome	Sugen/hypoxia rat model	Intravenous	(30)

NF-kB, nuclear factor kappaB; PLGA, poly(lactide-co-glycolide); PEG-PLGA, poly-(ethyleneglycol)-PLGA; MCT, monocrotaline; PLA, poly(lactide); PEG-PLA, poly-(ethyleneglycol)-PLA

4.1. Prostacyclin analog-incorporated NPs

We investigated the efficacy and safety of intratracheal administration of NPs incorporated with beraprost, a prostacyclin analog (beraprost-NPs) in Sugen-hypoxia-normoxia and monocrotaline (MCT) rat models of PAH **(Figure 1)**.(28) Nanoparticles of PLGA, a polymer, encapsulated with beraprost were used in that study. This type of nanoparticle can be used to achieve the sustained release of encapsulated drug, which takes place concomitantly with the degradation of PLGA. After a single administration, beraprost-NPs significantly decreased right ventricular pressure, right ventricular hypertrophy and pulmonary artery muscularization in both rat models. Beraprost-NPs significantly improved survival rate in the MCT rat model. No infiltration of inflammatory cells, hemorrhage or fibrosis was found in the liver, kidney, spleen and heart after administration of beraprost-NPs.

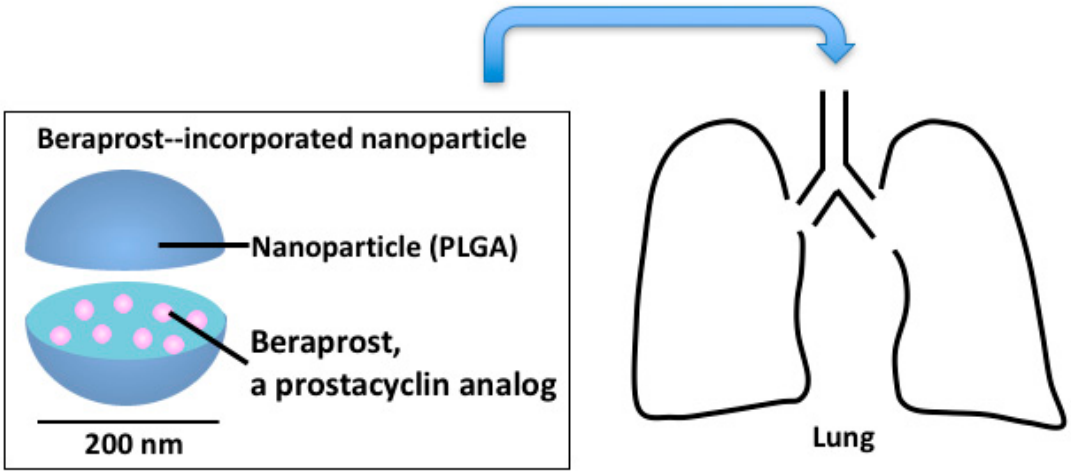

Figure 1. Prostacyclin analog-incorporated nanoparticles for treatment of pulmonary arterial hypertension.

Ishihara et al also reported that intravenous administration of beraprost encapsulated into nanoparticles prepared from a poly(lactide) homopolymer (PLA) and monomethoxy poly(ethyleneglycol)-poly(lactide) block copolymer protected against MCT-induced pulmonary arterial remodeling and right ventricular hypertrophy and that once per week intravenous administration of the beraprost-NPs also had an ameliorative effect on hypoxia-induced pulmonary arterial remodeling and right ventricular hypertrophy.(29)

4.2. Imatinib-incorporated NPs

We examined the efficacy of imatinib-incorporated NPs (Ima-NPs) in the MCT rat model of PAH and in human PAH-PASMCs.(28) A single intratracheal administration of Ima-NPs suppressed the development of MCT-induced PAH in rats. Ima-NPs had sustained antiproliferative effects on human PAH-PASMCs.

5. Summary and Clinical Perspective

In this review, we summarized the properties of selected nano-DDSs and the results of preclinical studies using the nano-DDSs in animal models of PAH. Drug-incorporated nanoparticles for local delivery might optimize the efficacy and minimize the side effects of drugs.

A phase I investigator-initiated clinical trial to test the efficacy of PLGA nanoparticle-mediated delivery of pitavastatin (UMIN000014940) has been completed. Future clinical trials may prove the safety and efficacy of a nano-DDS for PAH.

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Conflict of Interests

Drs. Nakamura received lecture fees from Bayer Yakuhin, Ltd., Pfizer Japan Inc., Nippon Shinyaku Co., Ltd., Actelion Pharmaceuticals Japan Ltd., Novartis Pharma K.K. and GlaxoSmithKline K.K.

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