Nitric Oxide-Donating Drugs for IOP Lowering

Subjects: Allergy

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Nitric oxide (NO) is a commendable new class of glaucoma drugs that acts on the conventional outflow pathway. An increasing number of nitric oxide donors have been developed for glaucoma and ocular hypertension treatment. Here, we will review how NO lowers IOP and the types of nitric oxide donors that have been developed.

glaucoma conventional outflow system intraocular pressure NO donors

1. Nitric Oxide-Donating Prostaglandins Analogues

Prostaglandins exhibit a wide range of physiological functions including smooth muscle regulation through interacting with its receptors [1][2]. There are nine PG receptors distributed in both the plasma membrane and nuclear envelope. Among them, FP and EP1–4 were expressed mainly in the uveoscleral tissue in the eye [1][3]. Prostaglandin F2α decreased IOP via FP and EP receptors stimulation, ciliary body (CB) relaxation and pressure-independent outflow increase [4]. Since latanoprost, the first PGF2α analogue, was approved by the FDA for open-angle glaucoma and ocular hypertension treatment in 1996, the use of prostaglandin analogues began to unfold, they offered one of the best IOP lowering effect for glaucoma patients. [4][5]. Prostaglandin analogues reduced IOP by inducing ECM remodeling in the sclera and ciliary muscle. Once FP receptors was activated, stimulation induced metalloproteinase (MMP) enzymes secretion which including MMP1 and MMP9. The MMPs worked by dissolving collagenase and increasing the outflow rate of aqueous humor by the pressure-independent pathway. On the other hand, endogenous prostaglandins synthesis induced by PLA2 stimulation also contributed to the ECM remodeling [1][6][7]. The PG analogues have also been reported to have better control of diurnal IOP compared with the nocturnal IOP, which might be due to the impact from nightly physiological fluctuations on the uveoscleral outflow [8].

In contrast to PG analogues, the modified PGs, NO-donating PGF2α analogues, including latanoprostene bunod (LBN) and NCX 470 showed better IOP lowering effects. They induced both uveoscleral outflow increase by FP receptor stimulation and conventional outflow increase by NO/sGC/cGMP activation [9][10][11]. Vyzulta, a 0.024% latanoprostene bunod eye drop synthesized by Nicox, has been approved by the FDA in patients with POAG and ocular hypertension for IOP reduction [1]. In general, the IOP lowering was achieve in two steps. First, under the action of esterase, LBN was divided into two parts—LA (latanoprost acid) and BDMN (butanediol mononitrate)—the former improved aqueous humour outflow facility via MMP secretion induced by FP receptor activation. Then the butanediol mononitrate was metabolized to NO along with 1,4-butanediol, a byproduct [6][7]. In three animal models, including the ocular hypertensive rabbits induced by hypertonic saline, the glaucomatous ocular

hypertensive dogs and the laser-induced ocular hypertensive, BOL-303259-X (also called as PF-3187207 or NCX 116) showed more significant effects in IOP reduction than latanoprost [12].

Clinical trials on the safety, tolerability and IOP lowering effect of latanoprostene Bunod (LBN) have been reported. In the phase 1 study, an open-label KRONUS clinical trial, 24 Japanese adult male subjects were selected according to the required standards of the experiment, and then the baseline of IOP was measured. After 0.024% LBN administration once a night for up to 14 days, the IOP was measured again and the effect of the medication on the subject was evaluated. The results showed that, compared with the baseline value, the IOP of the study group was significantly reduced. In this study, the common adverse reactions were conjunctival hyperemia and punctate keratitis [13]. In the phase 2 study, a dose-ranging study (VOYAGER) was conducted among 413 subjects with ocular hypertension (OHT) or open angle glaucoma (OAG), aiming to find the most suitable concentration of LBN for lowering IOP by comparing different concentrations of LBN and 0.005% latanoprost. Regarding the effect of IOP lowering, the 0.024% dose LBN (decreased by 34 percent) showed significantly better than 0.005% latanoprost did (30 percent). The results demonstrated an additional IOP lowering effect of LBN compared with latanoprost acid (LA) [14]. Another phase 2 trial (CONSTELLATION), among the twenty-four primary open-angle glaucoma and ocular hypertension subjects who participated in the experiment, latanoprostene bunod 0.024% solution showed better night-time IOP lowering effect than timolol maleate 0.5% solution [15]. In phase 3, clinical trials APOLLO and LUNAR were carried out among the subjects with ocular hypertension (OHT) or open angle glaucoma (OAG) in Europe and North America in order to further explore the safety and effectiveness of 0.024% LBN [16][17]. In the studies above, the timolol 0.5% treatment group was regarded as the control group. Both studies showed that after three months of administration, LBN 0.024% exhibited more significant effect in terms of lowering IOP than timolol 0.5%.

NCX 470, a NO donating PGF2α analogue molecule, was synthesized by transforming 15 hydroxyl within bimatoprost into 6-(nitrooxy) hexanoic acid via esterification [9]. In ocular hypertension and glaucoma animal models, NCX 470 showed more effective IOP reduction than bimatoprost. In addition, in both ONT-dogs (ocular normotensive dogs) and OHT-monkeys (ocular hypertensive monkeys), NCX 470 0.042% reduced IOP more than equimolar bimatoprost (0.03%) [9]. However, clinical results of NCX470 is to be released.

2. Nitric Oxide-Donating Carbonic Anhydrase Inhibitor

The carbonic anhydrase isoforms were expressed in the ciliary body. The isoforms CA I, II, IV and XII, are related to the aqueous humor secretion [18]. Carbonic anhydrase inhibitors (CAIs) were reported to lower IOP by up to 25–30% via inhibiting isozymes in the ciliary body, such as CA II and CA XII [19][20]. Systemic intake of the CAIs, such as acetazolamide, methazolamide and ethoxzolamidelowered IOP significantly. However, due to the ubiquitous distribution of the carbonic anhydrase in the body, systemic side effects, such as metabolic acidosis, weight loss and paresthesia at the extremities have been also frequently reported [21][22][23]. Despite the systemic side effects, CAIs have good application prospects for refractory glaucoma [24]. The good news is that newly developed CAIs have better water solubility and better corneal penetration, such as dorzolamide and brinzolamide, which made it possible to use topical drugs on the ocular surface and have fewer side effects than drugs administered

systemically [19][20][23]. However, dorzolamide still has side effects such as depression [25], nephrolithiasis [26], and allergic contact dermatitis (ACD) [27].

Several bi-functional compounds with a NO-donatng moiety bound to a dorzolamide scaffold demonstrated NO mediated effects in the vasculature [28]. Among them NCX 274 and NCX 278 showed ocular hypertensive effects in normotensive rabbits. NCX 274 consisted of a nitrate ester carried by a nitric oxide-donor linker with amino group of dorzolamide through amides, whereas NCX 278 was coupled with carbamates. NCX 274 showed a more powerful IOP lowering effect of NCX 274 than dorzolamide.

3. Nano-Material Based NO Donors

In contrast to classic NO donors, an increasing number of nano-material based NO donors have emerged aiming to overcome some of the inherent problems of NO donors, such as instability and a short half-life [29][30]. Nanoparticles based NO donors include silica nanoparticles, metal oxide nanoparticles, polymer coated metal nanoparticles and other kinds of nanomaterials (such as dendrimers, micelles) [31]. In additional to IOP lowering [32], it has a wide range of applications including wound healing [33][34], antimicrobial [35][36], cardiovascular diseases treatment [37][38][39][40], erectile dysfunction improvement [41], relieving liver fibrosis [42].

For silica nanoparticles, mesoporous silica nanoparticles (MSNs) and xxx were used as carrier for NO donors [43] [44]. Compared with nitroprusside (SNP) solution, the SNP@MSN system exhibited more efficacious and long lasting effect in IOP lowering [43]. With 1/40 dose, SNP@MSN increased IOP lowering effect from 3 hours to 48 hours. For hollow mesoporous organosilica (HOS) nanocapsules, it was biodegradable and can achieve trans-corneal co-delivery of hydrophobic NO donor JS-K (JR) and hydrophilic NO donor L-Arginine (LO) to the target tissues inside the eye [44]. HOS-J_RL_O was endogenous stimuli-responsive and was reduced and oxidized by ascorbic acid and catalysis of eNOS to release a large amount of NO molecules to lower IOP. It successfully treated ocular hypertension in three animal models. HOS-J_RL_O seemed to be a versatile, non-invasive, and efficacious treatment paradigm for precision glaucoma therapy.

Macromolecule composite NO carriers have been also developed to release NO. In β-gal-NONOate-loaded liposomes coated by β-galactosidase-loaded polymer, NO release was accomplished by the catalytic role β-galactosidase played in the catalysis of β-gal-NONOate. Results from C57BL/6 mice showed the conventional outflow facility within theβ-gal-NONOate-loaded liposomes treated group, which, under the effect of β-galactosidase, increased by 84% compared with the vehicle-treated group [45]. This invention gave a good example for NO delivery platform design. Recently, a new polymer combining super cation with GSH (glutathione) responsiveness (PEG-PAspTETA-SNO) was developed as carrier for NO [46]. PEG-PAspTETA-SNO showed more effective corneal penetration and significant IOP lowering effect in both C57BL/6 mice and eNOS knockout mice than the PEGPAspHMDA-SNO control group. Results from AAP cells indicated better uptake for PEGPAspTETA-SNO-RhoB (Rhodamine B labeled polymers) than PEG-PAspHMDA-SNO-RhoB control group. The endocytosis effect of PEG-PAspTETA-SNO-RhoB was inhibited by caveolae inhibitor mβ-CD, which indicated caveolae-Golgi may play a vital role in the PEG-PAspTETA-SNO induced endocytosis.

4. Other Kinds of NO Donors

The NO release from furoxan can be triggered by mercaptan cofactor. The function of substituents on the ring varied with its arrangement position. The third group of substituents is in charge of the total amount release of NO, and the fourth one is responsible for the balance of hydrophilic-lipophilic [47]. Blangetti et al. developed a big array of furoxan derivatives based on the basis above, the IOP lowering effects of which were tested in a transient ocular hypertensive rabbit model (tOHT). Some compounds showed similar IOP lowering effect to timolol after an hour of dosing. The study concluded that it was not the amount of NO released but the hydrophilic-lipophilic balance that determined the IOP lowering effects of such kinds of furoxan derivatives.

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