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KATP Channel Activation by Statins Decreases Intra-Ocular Pressure. Should We Explore These Channels as Therapeutic Targets in Glaucoma?

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Abstract

Introduction: This review discusses the molecular mechanisms responsible for the normalization of otherwise raised intraocular pressure (IOP) in patients of glaucoma when they are administered statin therapy. **Material and Methods:** Literature published between 1990 and 2016 on the pathophysiology of glaucoma and the action of statins has been reviewed. **Data Synthesis:** A decrease in resistance to aqueous humor flow through trabecular meshwork (TM) in the eye tissue results in lessening of the raised intraocular pressure. KATP channels have been discovered in the eye tissue recently. Activation of KATP channels facilitates the flow of aqueous humor through the TM. This presumption is strengthened by the action of statins. Statins activate these KATP channels and, thereby, facilitate the aqueous flow through TM leading to relief in IOP. Statins interfere in the cholesterol biosynthesis pathway leading to decreased cholesterol synthesis. However, a simultaneous decrease in the level of ubiquinone leads to activation of KATP channels. Further, accumulation of LC Acetyl CoAs also activates these KATP channels. **Expert Opinion:** Statins decrease the elevated intraocular pressure in glaucoma by activating KATP channels. KATP channels are recently discovered therapeutic targets which may be exploited in the treatment of glaucoma.

Keywords: KATP channels; Statins and pleiotropic effects; Statins and eye; Cholesterol biosynthesis; Iptakalim; Glaucoma pathophysiology and treatment.

- KATP channels have recently been discovered in the eye tissue.
- Activation of these KATP channels leads to a decrease in intraocular pressure.
- Statins inhibit cholesterol biosynthesis but in turn lead to accumulation of substrates, that is, the LC CoAs
- Interference in cholesterol biosynthesis pathway also results in decreased ubiquinone (CoQ) synthesis.
- Decreased ubiquinone levels and accumulated LC CoAs activate KATP channels present in the eye tissue leading to facilitation of flow of aqueous humor through trabecular meshwork.
- Use of KATP channels as therapeutic targets in the treatment of glaucoma may be a promising.

This box summarizes key points contained in the article.

1. Introduction

About 3.5% of world population between 40 to 80 years is suffering from OAG (Open Angle Glaucoma) [1, 2]. Since glaucoma is a progressive optic neuropathy leading to irreversible blindness, this high prevalence is significant and efforts to discover newer treatment modalities to retard its progression are being undertaken.

If a drug already in use for a particular indication is found to be effective for an altogether different ailment and is then therapeutically utilized for the same, it is called 'Drug Repurposing [3]. If statins are included in either the treatment or prevention of glaucoma, it would be a classic case of drug repurposing.

Statins are a group of drugs which inhibit 3 hydroxy 3 methylglutaryl coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is an enzyme critical in the cholesterol biosynthesis pathway [4]; and therefore, statins lead to inhibition of cholesterol synthesis in a rate dependent manner.

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A number of trials have demonstrated the beneficial effects of statins and proven beyond doubt that they reduce the morbidity and mortality from the cardiovascular and cerebrovascular events. This beneficial effect is both because of their lipid lowering action [5, 6] and the pleiotropic effects which are independent of lipid lowering.

How statins are able to decrease the raised IOP in patients of glaucoma is interesting because this group of agents seem to act upon the mechanisms involved in etio-pathogenesis of disease [7].

The pathophysiology and mechanisms involved in the etiology of glaucoma are under intense scrutiny, and KATP channels have been found to play an important role in the same. Since statins act on KATP channels and activate them; we propose that this action of statins leads to facilitation of flow of aqueous humor in the trabecular meshwork and thereby relief of raised intraocular pressure; a fact not discussed in literature so far.

This review will focus on KATP channels which play an important role in the etiopathogenesis of glaucoma. That statins exert their desired and beneficial therapeutic effects by acting on KATP channels shall be delved upon in detail. Mode of action of statins on KATP channels; and the mechanisms that lead to the activation of KATP channels by statins shall also be discussed.

2. Material & Methods

Literature published between 1990 and 2016 on the pathophysiology and treatment of glaucoma; and how statins may affect the same has been reviewed. A comprehensive search was carried out on Embase, PubMed and Cochrane databases using the search terms; pathophysiology and treatment of glaucoma; statins, pleiotropic effects of statins; statins and KATP channels.

3. Discussion and Data Synthesis

Statins have been found to normalize the raised IOP in patients suffering from glaucoma. The proposed mechanisms leading to these pleiotropic effects in glaucoma range from inhibition of isoprenylation of Rho-GTPase [8] to immunomodulation [9]. It has been proposed that by these actions, statins protect the retinal ganglion cells (RGCs) and thus damage from glaucoma [10]. However, confirmatory data for these presumptions is lacking.

Resistance to drainage of aqueous humor in the anterior chamber of eye is encountered at the juxta canalicular region of the trabecular meshwork, and at the basement membrane of the endothelium of the Schlemm's canal. Elevation of intraocular pressure occurs if resistance in the drainage system increases due to any cause. Proposed mechanisms for the increase in this resistance are 1) increase in cell contractility at trabecular meshwork 2) change in cell volume or 3) change in cell permeability [11-18].

The molecular mechanisms involved in the drainage of aqueous humor in trabecular meshwork cells are under extensive research. Recently, the role of KATP channels in ocular tissues has been studied [19]. Chowdhry et al have identified KATP channel openers (P 1075, nicorandil, diazoxide) as relatively new therapeutic agents which facilitate aqueous humor outflow in human anterior segment organ culture. Immunohistochemistry and RT-PCR studies have established the presence of KATP channel subunits (Kir 6.1, Kir 6.2, SUR 2A and SUR 2B) in the ocular tissues; and activation of these channels leads to increased aqueous humor flow.

Since statins decrease intraocular pressure but the mechanisms by which they do so is still unexplained till now, we propose that statins may be acting upon the KATP channels in the eye in a manner similar to the one which leads to their pleiotropic effects on the cardiac and vascular tissue.

3.1. The KATP Channels

KATP channels are ubiquitous in human body and most diverse of all the ion transporters. Adenosine triphosphote sensitive potassium channels (KATP) coordinate the membrane excitability with the metabolic state of the cell. The inhibition and activation of KATP channels is predominately dependent upon the micromolar concentration of intracellular ATP [20]. KATP channels have been implicated in glucose homeostasis in the hypothalamus, ischaemic preconditioning, cellular adaptation to stress, and in insulin secretion from β-cells. [21-25].

KATP channels are octameric proteins made up of a potassium inward rectifying tetrameric subunit (Kir 6.1 or Kir 6.2) surrounded by another tetrameric shell which contains sulphonylurea receptor subunits (SUR 1, SUR 2A, or SUR 2B). Kir 6.2/ SUR 1 channels form the functional unit in pancreatic β cells; and Kir 6.2/ SUR2B channels are found in the smooth muscle cells. The cardiac and skeletal muscle consist of Kir 6.2/ SUR 2A KATP channels. Several subunit combinations of KATP channels have been identified which confirm either to Kir 6.1 or Kir 6.2 [26-32].

Kir 6.1 containing KATP channels are found in the vascular smooth muscle; [33] whereas Kir 6.2 containing channels are present in non vascular smooth muscle [34]. In TM, the uveal, corneoscleral and juxtacanalicular regions contain Kir 6.1 subunit, whereas Kir 6.2 in present at much lower level. This suggests that in TM, the predominant Kir channel is 6.1. Further studies are needed to evaluate the prevalence and the type of KATP channels in the TM because Kir 6.1 and Kir 6.2 channels vary in conductance levels.

Chemical agents acting upon the KATP channels have been exploited as medications for various diseases. Activators of KATP channels like nicorandil and diazoxide find usage in treating angina and hypertension. [35, 36]. KATP channel inhibitors like sulphonylureas are widely used as anti diabetic medications [37].

Membrane permeability and functions of cells are dependent on the electrical activity of KATP channels [38-45]. Besides functions, the gap and junction in between the cells is also regulated by KATP channels [46-50].

3.2. Statins, the Cardiovascular System, and KATP Channels

Current view regarding as to how statins are able to exert their pleiotropic effects ranges from their anti-inflammatory effect [51-55] to their immunomodulating effect [56]. Enzyme Cox-2; involved in synthesis of thromboxanes, prostaglandins and the anti-inflammatory lipid lipoxins; is nitrosylated in a more facilitated manner because statins activate inducible nitric oxide synthase (iNOS). The actions of the lipoxin family of anti-inflammatory lipids are presumed to be partly responsible for the pleiotropic benefits of statins. Further, they also reduce the prenylations of various pro inflammatory modulators [57].

A more plausible explanation for the pleiotropic effects of statins is that they activate the KATP channel, a fact which has not been discussed in literature so far.

The role of pravastatin has been investigated after inducing ischemia in isolated rabbit hearts[58]. Pravastatin administration led to a marked improvement in the energy metabolism of myocardium and the statin achieved these beneficial effects by activating the KATP channels.

In another study [59] carried out on the actions of pravastatin on ventricular hypertrophy during remodeling after myocardial infarction, pravastatin administration led to favorable effects on the myocardium which were, however, abolished with the administration of glibenclamide. This implicates KATP channels as the target of pravastatin action because glibenclamide exerts its action by inhibiting these channels. Glibenclamide, a KATP channel inhibitor, abolishes the favorable effects exhibited by pravastatin on ventricular hypertrophy during remodeling. This suggests that pravastatin acts in a manner which is opposite to glibenclamide, a KATP channel inhibitor.

Pravastatin also protects against myocardial infarction because it activates KATP channels [60].

Besides pravastatin, statins like atorvastatin and cerivastatin also manifest endothelium dependent relaxation of preconstricted rat aorta [61-63]. This effect of cerivastatin is antagonized by glibenclamide. This suggests again that glibenclamide and statins act in a manner opposite to each other. The former inhibits KATP channels while the latter activates them.

3.3. Mechanisms Leading to Activation of KATP Channels by Statins

Flow Diagram-1 explains the molecular mechanisms which are involved in the activation of KATP channels by statins.

A) Cholesterol synthesis is reduced; but ubiquinone (CoQ) levels are also reduced simultaneously. (explained in Para-A,)

B) Accumulation of substrates which would have been involved in cholesterol biosynthesis pathway otherwise, but which now get accumulated because of the inhibitory action of statin therapy; also cause KATP channel activation. (explained in Para-B).

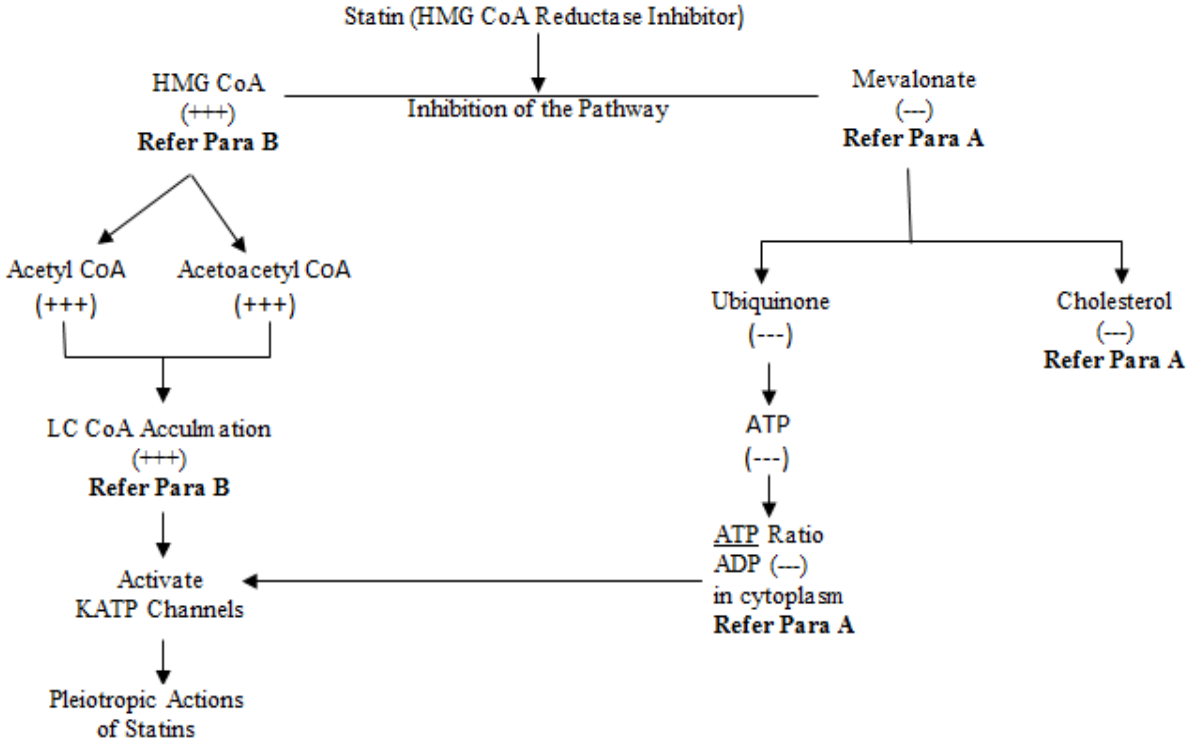
3.3.1. Para- A (Deficient production of ubiquinone)

Statins (HMG CoA reductase inhibitors) interfere in the cholesterol biosynthesis pathway leading to decreased production of cholesterol but therby increased accumulation of substrates like Acetyl-CoA and Acetoacetyl CoA [64]. Interference in the biosynthesis of cholesterol leads to decreased production not only of cholesterol but also of ubiquinone (CoQ enzyme) [65-68]. Since the ratio of ATP/ ADP determines KATP channels function, a decreased ATP would lead to activation of kATP channels.

3.3.2. Para- B (Accumulated substrates)

LC acyl CoAs activate KATP channels in the inside out patches which have been excised from β-cells of pancreas [69-71]. Kir 6.2 subunit is the target of acyl CoA action. LC Acyl CoA esters not only prevent the rundown of KATP channels, but also reactivate these channels after partial rundown. KATP channels are able to manifest activity even in absence of ATP if oleoyl CoA is present. The inhibitory effect of sulphonylureas on KATP channels is prevented by acyl CoA esters. The effects of oleoyl CoA are specific to KATP channels because oleoyl CoA does not prevent the rundown of cardiac inward rectifier channels [72]. In contrast, KATP channels in guinea pig cardiomyocytes are inhibited by palmitoleate and unsaturated fatty acid oleate. Unsaturated fatty acids have been shown to lead to inhibition of KATP channels in rat cardiomyocytes [73]. Elevation of LC-CoA esters and their products have significant effects on enzymes and ion channels [74]. Exposure of elevated long chain free fatty acids levels decreases glucose induced insulin secretion from pancreatic □-cells. These long chain acyl CoA esters (LC CoA) are the metabolically active form of free fatty acids and are responsible for decreased sensitivity in KATP channels for release of insulin when stimulated by glucose [75]. Patch clamp studies show that unsaturated and saturated LC-CoA lead to opening of KATP channels and this action is swift and reversible.

Flow Diagram-1. Depicting Mechanisms leading to activation of KATP channels by statins



3.3.3. Abbreviations & Signs Used in the Flow Diagram

+++	Accumulation	**HMG CoA**	3 hydroxy 3 methylglutharyl Coenzyme A
---	Deficiency	**LC CoA**	Long Chain Coenzyme A
		ATP	Adenosine Triphosphate
		ADP	Adenosine Diphosphate

3.4. The KATP Channels and the Eye

Demonstration of functional KATP channels in the trabecular meshwork of the eye (19)** is an exciting development. These channels have been found to increase outflow facility through the trabecular outflow pathway in human anterior segment organ culture, Also, a decrease in the IOP in brown Norway rat eyes is observed when they are activated by the KATP channel openers diazoxide, nicorandial and P1075.

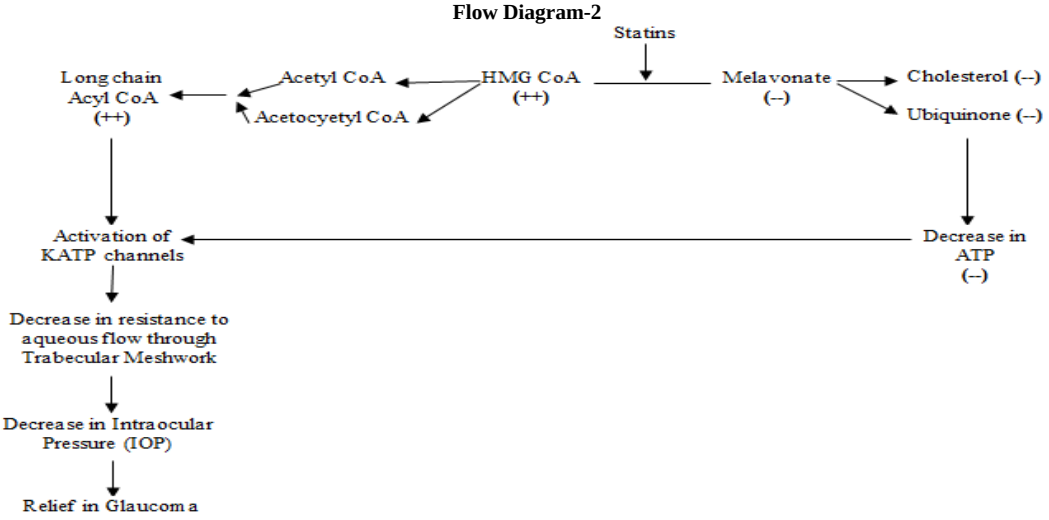
Statins being KATP openers, as discussed earlier, would also act in a manner similar to above mentioned KATP channel openers and lead to facilitation of outflow through trabecular outflow pathway and thereby decrease IOP.

Chowdhury, *et al.* [19] placed anterior segments from human eyes in perfusion organ culture and treated these segments with the KATP channel openers nicorandil, diazoxide and P1075, or with glibenclamide which inhibits KATP channels. The presence, functional state and specificity of KATP channels was determined by RT-PCR, immunohistocytochemistry and inside out patch clamp in human trabecular meshwork tissues. A rebound tonometer was used to measure the effect of diazoxide on IOP in Brown Norway rats.

The presence and specificity of function KATP channels subunits Kir 6.1, Kir 6.2, SUR 2A and SUR 2B was confirmed by electrophysiology. These channels have been found to exist in human trabecular meshwork (TM) tissue and normal human trabecular meshwork (NTM) cells. Diazoxide, a KATP channel opener, lowers IOP significantly in vivo.

How statins act upon KATP channels and thus decrease IOP has been explained in Flow Diagram-2.

Flow Diagram-2



4. Expert Opinion

i. That statins exert their pleiotropic effects by activating KATP channels is a subject which has not been discussed so far in literature. This review of literature summarizes the KATP channel activating effects of statins. Since glaucoma is fairly prevalent in the elderly age group; an age group where cardiovascular diseases are otherwise more common, administration of statins would have an added advantage because not only it would be beneficial in CVDs, but it would also be correcting glaucoma. Effect of statins in glaucoma is mild; but this observation suggests that research is needed to find specific pharmaceutical agents which act on the KATP channels in the eye tissue selectively and activate them.

Discovery of existence of ATP sensitive potassium channels in the trabecular meshwork in the eye tissue raises exciting possibilities in the treatment modalities of glaucoma. It is especially so because these KATP channels in the eye tissue have been found to be responsive to potassium channels openers. These KATP channels may be the new therapeutic targets in the treatment of glaucoma.

ii. KATP channels discovered in the trabecular meshwork and eye tissues confirm to the molecular configuration of subunits of Kir6.1/6.2 and of the splice variants SUR2A and SUR2B. KATP channels openers like chromokalim, diazoxide and P I075 activate these channels. Since the above mentioned drugs are more of experimental pharmaceutical agents and have not found favour in clinical usage because of the side effects in doses which activate KATP channels, newer KATP channel openers like Iptakalim [76] need to be subjected to trials in patients of glaucoma. Iptakalim is a relatively new KATP channel opener. Its structure differs from other KATP openers. Iptakalim exhibits selectivity for SUR 2B/Kir 6.1 channels and has relatively mild effects on SUR 2A/Kir 6.2 channels. More significantly it does not open SUR1/Kir6.2 channels. Potency of iptakalim for the SUR 2B/Kir 6.1 subtype of KATP channels is more than that of diazoxide and pinacidil. Also, iptakalim has been less studied as compared to these two which are the more extensively researched KATP channels openers. Iptakalim has a favorable safety profile and is tolerated well.

Use of Iptakalim, which was initially proposed as a newer pharmaceutical agent for hypertension, has now been extended to the field of psychiatry. Besides Iptakalim, other KATP channel openers exhibiting high selectivity to the KATP channels present in the trabecular meshwork of the eye may become future modalities in treatment of glaucoma.

iii. Oral therapy, rather than topical application, also will be an added option in the treatment.

iv. We suggest that long term prospective trials need to be conducted in patients of glaucoma after they have been initiated on statin therapy. Further, newer drugs which specifically and selectively activate these KATP channels be researched upon with an idea to exploit this untried and hitherto unused therapeutic target; that is the KATP channel.

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