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Role of the non-neuronal cholinergic system in the eye: A review

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Abstract

Pharmacologically active preparations directed towards modulating muscarinic receptor activity in the eye have been used for over 2000 years when extracts from *Atropa belladonna* were first applied to enhance eye appearance through pupillary dilation. The first clinically active drugs targeting a specific eye disease were anticholinesterases (e.g. ecothiophate) applied as eye drops to treat glaucoma in the 1960's. However, cataract was soon detected as a relatively frequent side effect and such drugs are now only used to treat glaucoma as a last resort. As muscarinic agonists have been found to reduce intraocular pressure both by decreasing aqueous humour production (through Na,K-ATPase pump inhibition) and increasing outflow (by muscle contraction), it is likely that treatments will be developed that target specific muscarinic subtypes. Recently, it has been shown that the M1 receptor subtype predominates in the lens. It is therefore important that this subtype is not targeted in future ocular therapies so that the side-effect of cataract is avoided.

Form-deprived myopia resulting from an increased axial length in the affected eye can be reduced by the application of atropine. This effect has been achieved both in a chick model system and in human clinical trials, and in the former system atropine has been shown to reduce the production of scleral extracellular proteins.

Carbachol stimulates tear fluid production through the activation of muscarinic receptors. Interestingly, at least part of the stimulation occurs via epidermal growth factor (EGF) receptors and although the precise signalling mechanisms are not completely understood, it has been shown that calcium mobilisation plays a critical role in both muscarinic and EGF receptor activity.

It should be noted that in the four examples described above, the cell types responsible for producing the physiological output are non-neuronal in origin. Therefore cholinergic receptor activation plays diverse roles in the eye and pharmacological intervention based on specific receptor sub-types has potential benefit in a number of ocular problems. However, potential side effects have also recently been identified.

Keywords: Muscarinic; Eye; Glaucoma; Myopia; Tears; Cataract; Calcium

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Introduction

Pharmacologically active preparations directed against cholinergic mechanisms have been applied to the eye for over 2000 years. The Egyptians realised the cosmetic value of extracts from *Atropa belladonna* and it is now recognised that atropine specifically targets muscarinic receptors. Atropine has been used routinely to induce pupil dilation during eye examinations, but a recognised side effect in some cases is an increase in intraocular pressure (IOP). This led to the idea of using acetylcholine analogues and acetylcholine-sparing drugs to reduce (IOP) [1]. However, it soon became recognised that such therapies (and anticholinesterases in particular) carried an increased risk of cataract formation [1] and alternative treatments are now available. There has recently been renewed interest in the application of muscarinic-based therapies in the treatment of glaucoma since it now appears that acetylcholine influences both the production and drainage of aqueous humour and so there is the possibility of dual control from one drug [2].

Cholinergic (and especially muscarinic) receptors have very wide roles to play in the eye, including eye growth [3,4], tear fluid production [5] and lens cell signalling [6]. The ocular cholinergic system is therefore being targeted in the treatment of form-deprived myopia and dry eye as well as glaucoma. As there are 5 recognised muscarinic subtypes [7], it will be necessary to identify which are present in the tissues to be targeted and which of these are responsible for the various clinical conditions. For example, muscarinic expression in the human lens has been characterised both by pharmacological and RT-PCR methods and an initial expression map has been prepared for selected ocular tissues [6].

Glaucoma

Intraocular pressure (IOP) is determined by the balance between aqueous humour production by the ciliary body cells and drainage at the Canal of Schlemm (Fig. 1A). Muscarinic receptor modulation provides a very powerful method of control as acetylcholine serves both to increase outflow [8] and inhibit inflow [2]. As the former mechanism simply involves muscular dilation of the Canal of Schlemm and is quite well understood [8], this review will concentrate on the more novel inhibitory mechanism. It has been known for some time that Na,K-ATPase provides the major energy source that drives fluid transport across the ciliary body and in fact the specific inhibitor, digoxin, induces a marked decrease in IOP [9]. More recently, it has become obvious that Na,K-ATPase activity can be modulated by a number of cytokines and neurotransmitters, including acetylcholine [2]. Using a direct measure of Na,K-ATPase activity in bovine ciliary extracts, Ellis et al. [2] have been able to elucidate the signalling pathway relating acetylcholine exposure to enzyme inhibition (Fig. 1B). They first established that a muscarinic system was involved by relieving the carbachol inhibition of Na,K-ATPase by atropine. They also showed that nitric oxide (NO) production was involved in two ways. Firstly, by blocking the carbachol-induced decrease in Na,K-ATPase activity by prior application of the nitric oxide synthase inhibitor N^{w}-nitro-L-arginine (L-NAME), and secondly by mimicking the carbachol-induced decrease with the artificial NO donor sodium nitroprusside (SNP). Carbachol also induced a significant increase in cGMP production within the tissue and this was abolished by 1H-[1,2,4] oxadiazolo [4,3-a] quinoxalin-1-one (ODQ), which is a selective inhibitor of soluble guanylate cyclase. The critical role of enzyme phosphorylation was revealed by exposure of the ciliary body to the phosphatase inhibitor okadaic acid, which mimicked the direct inhibition by carbachol. The cholinergic-NO regulation of Na,K-