The pharmacological effect of a beta-blocker on a local tissue e.g. the non-pigmented epithelium of the ciliary processes, the trabecular meshwork or the various ocular vascular beds, depends on a combination of several factors.

One of these factors is the concentration of the drug in a specific receptor-compartment which depends on the ability of the compound to cross a number of barriers in order to reach the receptors.

Other factors are the kind and number of different receptor types and subtypes present in the receptor compartment.

And last but not least there is the pharmacological profile of the betablocker itself.

The affinity of a beta-blocker for a beta-adrenergic receptor is a measure for its beta-blocking potency. Beta-1-selective beta-blockers like betaxolol have a higher affinity for beta-1-adrenoceptors than for beta-2-adrenoceptors while for non-selective beta-blockers like timolol the affinity is about the same for both receptor subtypes.

Fairly recently the existence of a third beta-adrenoceptor subtype was discovered. Because of some similarity in properties with the beta-2-adrenoceptor it is called a beta-2-like- or a beta-3-adrenoceptor. Some beta-blockers like (−)pindolol or (±)alprenolol and probably several others stimulate instead of block this receptor at concentrations far above those necessary to block beta-1 and beta-2 receptors.

These beta-blockers are called by Kaumann, non conventional partial agonists [1].

Beta-3-receptors are found in heart tissue and in blood vessels in coexistence with beta-2-receptors and having a similar effect on stimulation. This might also be the case in the non-pigmented epithelium of the ciliary processes, the epithelium of the trabecular meshwork and in retinal blood vessels were the existence of beta-2-receptors unambiguously has been demonstrated.

It is generally accepted that beta-blockers topically administered reduce the intra-ocular pressure by reducing the inflow of aqueous humor. Although it is tempting to assume that the mechanism of action is by blocking the beta-2-receptors of the non-pigmented epithelium of the ciliary processes, there are some serious objections to be made.
First of all there is no correlation between the potency of a beta-blocker to block beta-2-receptors in other tissues and its IOP lowering potency. The R(+) isomers of beta-blockers having generally a very low affinity for beta-2-receptors are still able to reduce the intraocular pressure. Secondly not all beta-blockers despite high concentrations in the aqueous humor effectively lower IOP.

However, there is a possibility that the beta-2-receptors in the epithelial membranes of the ciliary processes are at least partly beta-2-like receptors differing from the classical beta-2-receptors in other tissues of the body. Some evidence was recently presented by Nathanson [2].

Isoprenaline, a non-selective beta-agonist stimulates adeny late cyclase to produce c-AMP from ATP in heart tissue via beta-1-receptors and in the isolated ciliary process epithelium via beta-2-receptors.

This effect is blocked by beta-blockers (Table 1).

The optical isomer S(-) timolol used in ophthalmology as an IOP lowering agent does not discriminate between the beta-1 and beta-2 receptors as the potency ratio is about 1 in this biochemical test system.

However rather unexpectedly the S(-) isomer of betaxolol does not, and its enantiomer R(+) hardly discriminates between the two receptor types, while in other tissues the discrimination ratio varies between 100 and 250. The R(+) isomer of timolol in this test discriminates rather well between beta-1 and beta-2 receptors and is clearly a beta-2-selective antagonist. These data may explain why R(+) timolol as well as the clinically used S(-) timolol lowers the IOP as both are equipotent on beta-2-receptors of the ciliary processes epithelium.

On the other hand the data on betaxolol show that at least part of the receptor population of the ciliary processes epithelium consists of beta-2-like receptors which may play a role in the IOP lowering mechanism of beta-blockers whether they are beta-1-selective or not.

Also in cultured human trabecular meshwork cells the beta-2-adrenoceptor population may consist at least in part of beta-2-like receptors as can be inferred from data given by Polansky [3].

From this data (Table 2) it appears that the affinity of betaxolol for the beta-2-receptors in this tissue (K_d = 40–60 nM) is about 4 times higher than in

<table>
<thead>
<tr>
<th></th>
<th>Heart</th>
<th>Ciliary process</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Timolol</td>
<td>0.0064</td>
<td>0.0055</td>
<td>1.2</td>
</tr>
<tr>
<td>R-Timolol</td>
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<td>0.0045</td>
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<tr>
<td>S-Betaxolol</td>
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<td>0.15</td>
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<tr>
<td>R-Betaxolol</td>
<td>90.0</td>
<td>29.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Table 1. Isoprenaline (beta-agonist) stimulated adeny late cyclase in heart (beta-1) and ciliary process (beta-2) blocked by beta-blockers. (From [2])