ROLE OF THE CANNABINOIDS IN GLAUCOMA

PAPEL DE LOS CANNABINOIDES EN EL GLAUCOMA

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In recent decades we have witnessed substantial developments in the knowledge about pathophysiology of glaucoma as well as innovative diagnostic and early progression detection techniques. We have also seen technical progress in surgical and laser treatments for some types of glaucoma. However, for medical treatments we continue to avail ourselves with the same range of drugs. This makes us responsible for researching new ways to reduce intraocular pressure and also develop neuro-protective effects for ensuring adequate control of patients who become refractory to the effect of available resources in order to avoid glaucomatous progression.

In the seventies a high number of studies on cannabinoids applied to glaucoma were published after identifying a clear ocular pressure-reducing effect (5-45% reduction of IOP) in a sample of volunteers who ingested or smoked marihuana (1). However, this effect had a mean duration of 3-4 hours and therefore required frequent administration to maintain stable pressure values. Subsequently, additional studies utilizing different administration routes were published, achieving similar effects on IOP. It was confirmed that the main active ingredient and the one with the highest psychotropic effect of marihuana (delta-9-tetrahydrocannabinol) reduced IOP when administered through the IV route, orally or inhaled. To account for the dosage-dependent ocular pressure reducing effect, the identified responders were cannabinoids in 60-65% of the population, drawing these conclusions from a sample with healthy volunteers and glaucoma patients (2).

We can also find an abundance of studies demonstrating a neuro-protective effect of cannabinoids. Tetrahydrocannabinol has proved to reduce the neuro-degenerative effect in brain ischemia rat models. The beneficial effect of cannabinoids has also been demonstrated in reduced secondary degeneration associated to glaucoma regulated by the excit-toxicity of glutamate. This effect was reproduced in experimental models in which the ganglionic cells were subjected oxidative stress.

Even though the precise action mechanism of cannabinoids on ocular phisiology is not yet fully known, studies published in the nineties described the two main cloned cannabinoid receptors, i.e., rCB1 and rCB2, with the former being the main ocular receptors. It was proposed that these receptors had the effect of reducing the production and increasing the excretion of aqueous humor through the trabecular mesh and the uveo-scleral pathway. This effect is compatible with the finding of high concentrations of said receptors in the stroma and non-pigmentary epithelium of the ciliar body, the blood vessels of said body, the ciliar muscle and the trabecular mesh. Said receptors have also been identified in different retinal structures, with particularly intense markings at the level of the external photoreceptor segments and the internal, external and nuclear internal plexiform layers, as well as associations to ganglionic, amacrine and horizontal cells (3).

It was also proposed that the neuro-protective effect occurs mainly through the activation of CB1-type receptors, the neuro-protective function of which occurs due to the inhibition of voltage-dependent calcium channels. However, it is not entirely clear that the neuro-protective effect brought about by cannabinoids is found exclusively at the level of CB1 receptors because the use of CBD, a non-psychotropic cannabinoid which does not activate the CB1 receptors, also demonstrated a neuro-protective effect in vivo by blocking the formation of nitro-thyrosine. In addition, cannabidoile not only has neuro-protective effects on its own, it

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also inhibits the degradation of endogenous cannabinoi
d, i.e., arachinodyl ethanolamide or anandamid-
(4).

Notwithstanding the beneficial effects in the con-
text of glaucoma, cannabinoids are not free of unde-
sired effects: the administration of most drugs
belonging to the cannabinoid family entail adverse
systemic effects such as low blood pressure, tachy-
cardia, palpitations and psycho-motor alterations.
At the ocular level, said drugs bring about a sustai-
ned contraction of the ciliar muscle, associated to a
reduction of the accommodation range and corneal
opacities.

In the light of said secondary effects, researchers
began exploring topical application. The first obsta-
acle was the high lipo-sollubility of said compounds
which inhibited adequate dissolution as well as
absorption thereof. This obstacle was reduced by the
use of cyclodextrines, producing highly encouraging
results. Thus, Porcella et al (5) demonstrated the
ocular pressure-reducing effect of a cannabinoid
synthetic agonist (WIN552122) when administered
topically in voluntary patients refractory to conven-
tional medical therapies. Prior to the development
of this study, the absence of topical and systemic
secondary effects was verified in healthy volunteers.

These findings about the positive effect of canna-
binoids as ocular pressure reducing and neuro-pro-
tective agents increase our hopes about the role they
could play in glaucoma. However, to confirm their
safety and efficacy clinical trials are needed to
assess the applicability of cannabinoids in our daily
clinical practice.

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