Nick Lane

Cannabis and glaucoma - The inside story

Nick Lane PhD

Despite their emotive political and social context, clinical trials of cannabis extracts have been decidedly small-time. The first reports that marijuana lowers IOP date back to the early 1970s, yet there has been remarkably little clinical progress since then. However, endogenous cannabinoids are now beginning to yield striking insights into glaucoma, raising novel treatment possibilities.

Political pressure groups have made a big fuss about the benefits of marijuana smoking for glaucoma, but the real impact on treatment has been negligible. A 2002 study, for example, showed that only five per cent of more than 1000 consecutive patients who were referred to two urban glaucoma practices in the US used any form of complementary or alternative therapy at all. In that study, not one patient smoked marijuana, nor indeed used any form of cannabinoid.

Perhaps they were all put off by the highly publicised comments of researcher Dr Keith Green PhD, DSc, who caused a furore back in 1998 when he calculated that patients would need to smoke a joint every three or four hours, for a total of around 3,500 a year, to keep their IOP under control. Clearly the long-term side effects – notably emphysema and altered cognitive function – make this hardly a recommendable option.

Yet beneath the painfully slow clinical progress, there's been a hive of activity in the underworld of research. Back in the 1970s, there were a few hundred papers a year on cannabinoids; last year, well over 6000. The emphasis has changed from smoking marijuana to the molecular mechanics within – the endocannabinoids and their receptors now hold most interest and potential.

Ironically, the first drug targeting endocannabinoid receptors to be licensed in Europe is an antagonist, rather than an agonist – rimonabant (Acomplia, Sanofi/Aventis) was approved by the EMEA last year as an adjunct to diet and exercise for overweight or obese patients with associated risk factors, such as Type 2 diabetes or dyslipidaeamia.

But this was the first of what may turn into a rush. In the last year or two, cannabinoid receptors have been found to underpin several utterly unexpected diseases, including osteoporosis, atherosclerosis and Parkinson's disease, as well as the usual suspects for a psychotropic drug, like schizophrenia and susceptibility to substance abuse. And there is good evidence that cannabinoids play a multifaceted role in the pathophysiology of glaucoma too.

Augusto Azuara-Blanco MD, FRCS (Ed), PhD, at the Aberdeen Royal Infirmary, told *EuroTimes*, "Although there are only a few groups working directly on glaucoma, there are many others working on related areas, like the pharmacology and cell biology of cannabinoids, and their role in neuroprotection, which is of course closely allied to glaucoma. I think we may well see a major breakthrough in glaucoma soon."

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George Kunos MD, PhD

George Kunos MD, PhD, at the NIH, concurs. "I've been around for a while", he confessed to *EuroTimes*. "Back in the early 1980s I was there in the heyday of research into endogenous opioids. But the endogenous cannabinoids seem to me far more important – they're critical to the regulation of a large number of physiological functions that underpin health and disease, and they might also be playing an important role in degenerative conditions like glaucoma."

The Holy Trinity

There are two main classes of cannabinoid receptors, known as CB1 and CB2. The CB1 receptors are found mostly in the central nervous system, and these are linked with the psychotropic side effects of cannabis. The CB2 receptors are found mainly in the periphery, notably in the immune system, but are also found sparingly in the brain. In addition, some evidence suggests the existence of a third group of receptors, whose properties are as yet dimly perceived, but which may prove to be equally important.

Both the CB1 and CB2 receptors have been found in the eye, in several tissues linked to glaucoma. According to Dr Zhao-Hui Song PhD, at the University of Louisville, Kentucky, both receptor types are found in the trabecular meshwork, accounting for the greater part of cannabinoid IOP reduction. Dr Song and his team have shown that selective cannabinoid agonists such as noladin ether reduce IOP through their effect on the endocannabinoid receptors in the trabecular meshwork.

"Both CB1 and CB2 receptor agonists have a direct effect on the morphology, adhesion and migration of trabecular meshwork cells," he told *EuroTimes*. "CB1 and CB2 receptor signalling affects the cytoskeleton, causing the cells to 'round up' and become less mobile. This in turn may lead to the reduction in IOP by increasing outflow through the meshwork."

But of course IOP is only part of the problem in glaucoma, and the real buzz about the cannabinoid receptors is that they are also found in other cell types linked to glaucoma – the retinal ganglion cells, and the glial cells at the optic nerve head. This means that targeting the cannabinoid receptors has the potential to interfere with all three prongs of the glaucoma trinity – raised IOP, neurodegeneration and excavation of the optic nerve head.

The degeneration of retinal ganglion cells has long been linked with glutamate excitotoxicity, but the underlying cause is still uncertain. One factor is the absorption of light by the abundant mitochondrial proteins in the ganglion cells, converting them into potent free-radical generators, as proposed by Prof Neville Osborne in *EuroTimes* last year.

The free-radical species most incriminated in ganglion cell death is peroxynitrite, formed when nitric oxide reacts with a superoxide radical. In this context, it's interesting that cannabinoids such as delta-9 THC can protect retinal ganglion cells against peroxynitrite toxicity via a mechanism that involves the CB1 receptors.

The reason it works is that peroxynitrite is only formed when there's plenty of nitric oxide around, which in turn is formed via the enzyme nitric oxide synthase – a calcium-dependent enzyme. Last October, Dr Melanie Kelly PhD, and her colleagues at Dalhousie University, Canada, showed that cannabinoids inhibit calcium signalling in rat retinal ganglion cells. This in turn should block nitric oxide formation, and so protect ganglion cells against excitotoxicity.

Dr Song notes that glial cells – microglia and astrocytes – in the optic nerve head also express both CB1 and CB2 receptors. The effect of cannabinoids on glial cells may parallel their effects on trabecular meshwork cells.

"By altering the dynamic properties of the cytoskeleton, cannabinoids may tone down glial cell adhesion, migration and activation," Dr Song told *EuroTimes*. "That in turn means that the immune or inflammatory attack on cells in the optic nerve head may be abrogated."

The question is what can be done about it all? If the clinical experience with cannabinoids has been less than salutary, that is largely down to the difficulties of controlling their pharmacology. While the psychotropic effects of cannabinoids are limited to the CB1 receptors, these receptors do seem to play the largest role in glaucoma. Topical applications of cannabinoids in the eye have a tendency to find their way into the systemic circulation; and there is also the threat of tolerance, at least with some of the many cannabinoids.

Current research suggests there is more than one binding site on the CB1 receptor. This raises the possibility that some agonists could activate the CB1 receptors without necessarily causing the psychotropic side effects, although this has not been demonstrated to date.

Another possibility is to rely on the endogenous cannabinoids, whose distribution about the body is far from equal. Last month for example, Dr Robert Malenka, MD, PhD, and his colleagues at Stanford University reported a potential breakthrough in the treatment of Parkinson's disease in *Nature*, using mice.

Rather than battering the whole system with exogenous cannabinoids, Malenka and colleagues used a drug (URB597, Kadmus Pharmaceuticals) that slows the enzymatic breakdown of endocannabinoids in the brain. When URB597 was combined with a dopamine mimetic, Dr Malenka noted, the results were striking: "The animals really improved dramatically."

Blocking the breakdown of endocannabinoids in the eye might well be a way forward, Dr Kunos said. He cited a study that found lower levels of endocannabinoids in ocular tissues of glaucoma patients – notably the trabecular meshwork and retina.

"If the levels of endocannabinoids are lower, it might be possible to selectively target the deficient tissues using an inhibitor of endocannabinoid breakdown," Dr Kunos told *EuroTimes*.

But if bolstering the faltering levels of endogenous cannabinoids is a way of slowing glaucoma, then might alterations in the endocannabinoid system be part of the problem in the first place? Could it be that genetic variations in the endocannabinoid system underpin susceptibility to glaucoma? After all, there has never been a clear causal link between the three prongs of the glaucoma trinity – raised IOP, neurodegeneration and excavation of the optic nerve. Alterations in the cannabinoid receptors or their endogenous agonists might provide just such a link.

Receptor deceptor

A large number of mutations and polymorphisms have been found in the genes for CB1 and CB2, but little is known yet about their associations with common diseases.

The first, and surprising, indication of how important they might be came in 2005, when Prof Andreas Zimmer PhD, and colleagues at the University of Bonn, discovered a link with osteoporosis. Post-menopausal women with a single-nucleotide polymorphism in the gene for CB2 were more likely to suffer from osteoporosis than age-matched controls ($P = 0.0001$). In contrast, there was no association with polymorphisms in the gene for CB1.

The Bonn group then dropped another bombshell, linking polymorphisms in CB2 with atherosclerosis in mice and men. They initially showed that CB2 activation could slow the development of plagues in mice (published in *Nature* in 2005), through a mechanism partly dependent on blocking macrophage migration and activation. Then they noted an association between atherosclerosis and osteoporosis in human populations.

Professor Zimmer commented, "It is tempting to speculate that CB2 polymorphisms contribute to the etiology of both disorders, thus providing one explanation for the association of atherosclerosis with osteoporosis."

So what about glaucoma? Prof Zimmer unfortunately declined to proffer an opinion. In January this year, though, Priya Duggal PhD, and her colleagues at the NIH published a major study of novel genetic loci associated with raised IOP, based on a genome-wide scan of the Beaver Dam Eye Study. They reported six candidate regions that are associated with raised IOP, though as yet none of them have been pinpointed to a particular gene.

"From our genetic study, I think it's unlikely that the CB1 or CB2 loci are responsible for the genetic peaks. Having said that, it's still quite possible that either, or even both of the cannabinoid receptor genes are involved in glaucoma. What we need are candidate gene association studies to link the receptor genes with glaucoma or raised IOP," Dr Duggal told *EuroTimes*.

The other possibility is messier – it's not the receptors but the endocannabinoids themselves that are altered in glaucoma. The fact that tissue levels of endocannabinoids are lowered in glaucoma does hint at the possibility of some kind of genetic deficiency, but the fact that endocannabinoid levels are low in some ocular tissues and not in others suggests a complex regulatory context.

Worse still, the biochemical pathways by which endocannabinoids are synthesised are elaborate, and closely linked to lipid metabolism, especially that of arachidonic acid. Arachidonic acid is a precursor of leukotriene and prostaglandin synthesis, so there is a potential link between endocannabinoids and inflammation. It is feasible that dietary treatments, such as taking high doses of omega-3 fatty acids from fish oils, could intervene in endocannabinoid metabolism too.

Indeed, Dr Kunos told *EuroTimes*, "Endocannabinoids can be synthesised from omega-3 fatty acids, but how their properties compare is frankly anybody's guess at the moment."

With such complexity, it may be some time before the role of endocannabinoids in glaucoma is fully appreciated, and optimal treatment paths established. But if there was irony in the first drug targeting the cannabinoid receptors being an antagonist rather than an agonist, that irony has a grave edge. If a failure of the endocannabinoid system is a causal factor in glaucoma, then actively inhibiting the CB1 and CB2 receptors might exacerbate or even provoke glaucoma. And although glaucoma is usually a chronic degenerative condition, changes in IOP could potentially happen quite quickly.

"Obesity is a common condition. In the near future there could be a large patient cohort taking a CB1 antagonist/inverse agonist. If endogenous cannabinoids are important for maintaining IOP, then a CB1 antagonist/inverse agonist will have the potential – admittedly it's only a theoretical potential – to raise IOP and induce glaucoma. I think at the very least that ophthalmologists should be wary, and keep an eye on IOP in patients being treated for obesity," Dr Song told *EuroTimes*.

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