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## PERSPECTIVE

## Cannabinoids and glaucoma

I Tomida, R G Pertwee, A Azuara-Blanco

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Glaucoma is one of the leading causes of blindness in the world. In spite of the diverse therapeutic possibilities, new and better treatments for glaucoma are highly desirable. Cannabinoids effectively lower the intraocular pressure (IOP) and have neuroprotective actions. Thus, they could potentially be useful in the treatment of glaucoma. The purpose of this article is to provide the reader with an overview of the latest achievements in research into the potential use of cannabinoids for glaucoma.

without medical supervision. Recently, several states have legalised the medical use of cannabinoids. In the United Kingdom, cannabis is registered as a schedule I—class C drug.<sup>1–4</sup> The medical use of cannabinoids is currently restricted to dronabinol (Marinol, synthetic  $\Delta^9$ -tetrahydrocannabinol) and nabilone; these drugs are administered orally as anti-emetics and appetite stimulants for patients with AIDS or on chemotherapy. Other potential clinical applications for cannabinoids, including glaucoma therapy, are currently under intense investigation (see below).

## PHARMACOLOGY

The cannabis plant has more than 480 chemical constituents.<sup>5</sup> Of these, there is a group of at least 66 compounds that contain only carbon, hydrogen, and oxygen and are known collectively as cannabinoids. The remaining constituents of cannabis include nitrogenous compounds such as amino acids, proteins and glycoproteins, sugars, hydrocarbons, alcohols, aldehydes, ketones, simple acids, fatty acids, esters and lactones, steroids, terpenes, non-cannabinoid phenols, flavonoids, pigments (carotene and xanthophylls), and vitamin K. Terpenes are thought to be responsible for the characteristic odour of cannabis plants (fig 1). The main psychoactive constituent of cannabis is the cannabinoid,  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), the structure of which was determined by Gaoni and Mechoulam in the 1960s (fig 2).<sup>5</sup> Most research into the pharmacological properties of plant cannabinoids has focused on this cannabinoid and, indeed, with the exception of cannabinal and cannabidiol (figs 2 and 3), other plant cannabinoids have been subjected to little or no pharmacological research.<sup>6,7</sup>

It is now generally accepted that  $\Delta^9$ -THC produces many of its effects by acting through cannabinoid receptors of which there are at least two subtypes, CB<sub>1</sub> and CB<sub>2</sub>.<sup>8</sup> Both subtypes are coupled through G<sub>i/o</sub> proteins, negatively to adenylate cyclase and positively to mitogen activated protein kinase. In addition, CB<sub>1</sub> receptors are positively or negatively coupled through G<sub>i/o</sub> proteins to certain calcium and potassium channels. CB<sub>1</sub> receptors, which were cloned in 1990, are present in brain, spinal cord, and certain peripheral tissues that include lung, heart, urogenital and gastrointestinal tracts, and the eye.<sup>9–11</sup> Many CB<sub>1</sub> receptors are present on central and peripheral neurons, one of their functions being the modulation of neurotransmitter release. CB<sub>2</sub> receptors, cloned in 1993, seem to be located especially in cells and tissues associated with the immune system, such as the tonsils, spleen, and different types of

Cannabis/marijuana is the most frequent illicit drug used today for recreational purposes. Yet it is not widely known that the cannabis plant (*Cannabis sativa*; Latin for “planted hemp”) (fig 1) is one of the oldest drugs used for medical purposes. Its therapeutic use was first recorded in a classical medicine book by the Chinese emperor Shen Nung in 2737 BC. The medical use of cannabis was also known in other ancient cultures throughout India, Assyria, Greece, Africa, South America, Egypt, and the Roman Empire.<sup>1</sup>

Cannabis was introduced on a larger scale into Western medicine during the 19th century, primarily by British doctors. They accumulated experience in the use of “Indian hemp” while working in the colonies, recommending it as an appetite stimulant, analgesic, muscle relaxant, anticonvulsant, and hypnotic. In 1839, Dr William Brooke O’Shaughnessy, an Irish physician at the Medical College of Calcutta, published a detailed report “On the preparations of the Indian Hemp or Gunjah.” After performing animal studies, he determined that cannabis preparations were safe and effective in treating rabies, rheumatism, epilepsy, and tetanus. The Ohio Medical Society of Physicians reported in 1860 successful treatment of “stomach pain and gastric distress,” psychosis, chronic cough, gonorrhoea, and neuralgia with cannabis. The plant was difficult to store, its extracts were variable in potency, and the effects of oral ingestion were not constant. Other new drugs were becoming available in the early 1900s with more reliable effects, and cannabis began to be misused for recreational purposes. The American Marijuana Tax Act of 1937 intended to prevent non-medical use, but made cannabis difficult to obtain for medical purposes too, and it was subsequently removed from the US pharmacopoeia in 1942.

In the United States cannabis is now classified as a schedule I drug, regarded as having high potential for abuse, and to be unsafe to take

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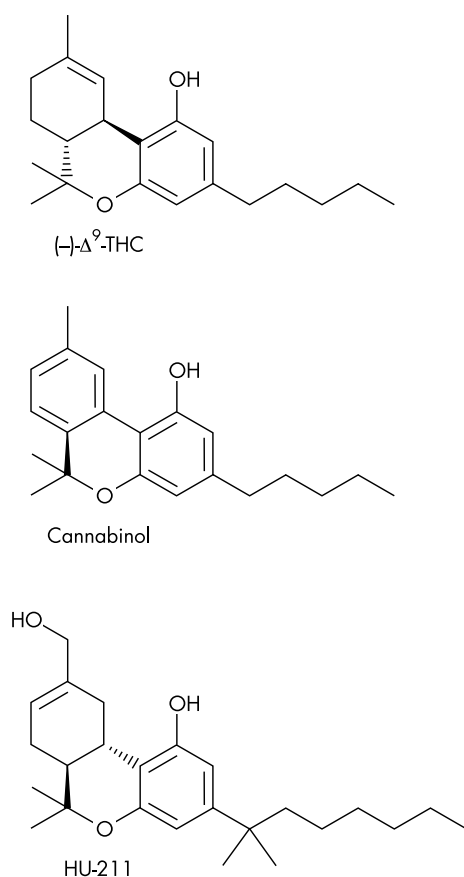
**Figure 1** Photograph of the *Cannabis sativa* plant (provided by GW Pharmaceuticals, Wiltshire, UK)

leucocytes.<sup>8,9</sup> One role of these receptors is modulation of cytokine release.

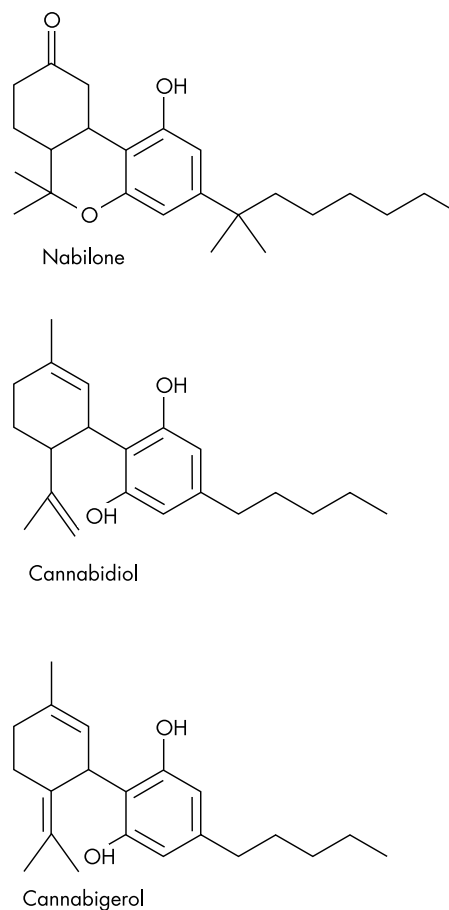
Endogenous agonists for cannabinoid receptors have also been discovered; this system of “endocannabinoids” and receptors constituting what is now generally known as the endocannabinoid system.<sup>12</sup> The endocannabinoids that have been identified to date are all analogues of arachidonic acid. They include arachidonoyl ethanolamide (anandamide; AEA), 2-arachidonoyl glycerol (2-AG) which bind more or less equally well to CB<sub>1</sub> and CB<sub>2</sub> receptors, and 2-arachidonoyl glyceryl ether (noladin) which is CB<sub>1</sub> selective (fig 4). AEA behaves as a partial cannabinoid receptor agonist with less CB<sub>2</sub> than CB<sub>1</sub> efficacy. Within the nervous system, endocannabinoids are synthesised and released by neurons on demand, functioning as neurotransmitters or neuromodulators. There is also evidence that endocannabinoids serve as

retrograde synaptic messengers.<sup>12</sup> Following their release, the effects of at least some endocannabinoids are thought to be rapidly terminated by cellular uptake and intracellular enzymatic hydrolysis.<sup>13</sup>

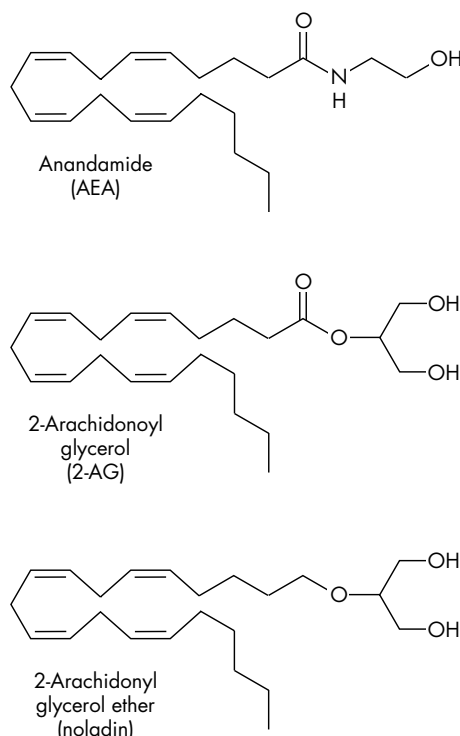
As detailed elsewhere<sup>6,8</sup> some established cannabinoid receptor agonists bind more or less equally well to CB<sub>1</sub> and CB<sub>2</sub> receptors, important examples being WIN55212-2, which has marginally greater CB<sub>2</sub> than CB<sub>1</sub> affinity, and  $\Delta^9$ -THC, HU-210, CP55940, and nabilone (fig 3). As to CB<sub>1</sub> selective agonists other than noladin, these include the anandamide analogues, methanandamide, O-1812, arachidonyl-2'-chloroethylamide (ACEA), and arachidonylcyclopropylamide (ACPA). Examples of CB<sub>2</sub> selective agonists are the THC analogues, L-759633, L-759656, JWH-133 and HU-308. Selective CB<sub>1</sub> and CB<sub>2</sub> receptor antagonists have also been developed, the most important of these being the CB<sub>1</sub> selective SR141716A, AM251, AM281 and LY320135, and the CB<sub>2</sub> selective SR144528 and AM630.<sup>8</sup> There is evidence, however, that these compounds are not “silent” antagonists.<sup>14</sup> Thus, as well as attenuating the effects of CB<sub>1</sub> or CB<sub>2</sub> receptor agonists, they can by themselves elicit responses in some cannabinoid receptor-containing tissues that are opposite in direction from those elicited by CB<sub>1</sub> or CB<sub>2</sub> receptor agonists. While some of these “inverse cannabinimimetic effects” may be attributable to a direct antagonism of responses elicited at cannabinoid receptors by released endocannabinoids, there is evidence that this is not the only possible mechanism and that these compounds are in fact all inverse agonists that can reduce CB<sub>1</sub> or CB<sub>2</sub> receptor constitutive activity.



**Figure 2** Chemical structure of typical classic cannabinoids  $\Delta^9$ -tetrahydrocannabinol, cannabinol, and HU-211.



**Figure 3** Chemical structure of nabilone, cannabidiol, and cannabigerol.



**Figure 4** Chemical structure of endogenous cannabinoids anandamide (AEA), 2-arachidonoyl glycerol (2-AG), and 2-arachidonoyl glyceryl ether (noladin).

AEA activates vanilloid (TRPV1) receptors in addition to CB<sub>1</sub> and CB<sub>2</sub> receptors and there is also growing evidence for the existence of non-CB<sub>1</sub>, non-CB<sub>2</sub>, non-vanilloid pharmacological targets for AEA and/or other cannabinoids.<sup>8, 15</sup> There is evidence too that classic cannabinoids such as  $\Delta^9$ -THC, HU-211, and CBD have antioxidant properties (see below).<sup>7, 16–18</sup> In addition,  $\Delta^9$ -THC can act through presynaptic CB<sub>1</sub> receptors in the CNS to inhibit glutamic acid release and that HU-211 can block glutamate (NMDA) receptors.<sup>8, 18</sup>

As well as showing therapeutic potential as neuroprotective agents,  $\Delta^9$ -THC and CBD have other potential clinical applications, as indeed does the CB<sub>1</sub> receptor antagonist/inverse agonist, SR141716A.<sup>7, 18–20</sup>  $\Delta^9$ -THC, for example, is already used in the clinic as an appetite stimulant and anti-emetic.<sup>18</sup> In addition, this cannabinoid will most likely prove to be useful as an anti cancer drug<sup>21</sup> and for the management of pain,<sup>22, 23</sup> and of various kinds of motor dysfunction that include the muscle spasticity, spasm, or tremor associated with multiple sclerosis and spinal cord injury,<sup>24</sup> the tics and psychiatric signs and symptoms of Tourette's syndrome, and the dyskinesia that is produced by L-dopa in patients with Parkinson's disease.<sup>25–27</sup> As now discussed, one other important potential clinical application for cannabinoids, is the management of glaucoma.

## CANNABINOIDS AND GLAUCOMA

In 1971, Hepler and Frank reported a 25–30% IOP lowering effect of smoking marijuana in a small number of subjects.<sup>28</sup> The duration of action of marijuana after smoking was relatively short, about 3–4 hours, and there seemed to be a dose-response relation.<sup>28, 29</sup> Other ocular effects were observed such as conjunctival hyperaemia, reduced tear production, and change in pupil size.<sup>29</sup> Acute systemic side effects induced by marijuana smoking included reduction of systemic blood pressure and tachycardia.<sup>4</sup> Psychotropic effects were very variable and included euphoria or

dysphoria, disruption of short term memory, cognitive impairments, sense of time distortion, reduced coordination, and sleepiness.<sup>4</sup>

An earlier report on the effect of smoked marijuana indicated the possibility of tolerance. Thus, the IOP reduction appeared to be inversely related to the duration of marijuana use.<sup>30</sup> In contrast, Dawson *et al*<sup>31</sup> reported on their ophthalmological findings comparing non-users with long term users of marijuana (10 years or more). After applying the water loading test to both groups, the reduction of IOP associated with marijuana treatment was similar between users and non-users.

Since these early observations numerous studies have been conducted confirming that different cannabinoids, including cannabidiol, cannabigerol, endogenous cannabinoids, and some synthetic cannabinoids, can reduce the IOP when administered systemically and topically (see below). Obviously, smoking of marijuana is not advisable as a long term treatment. In addition to the acute side effects, long term marijuana smoking is associated with emphysema-like lung changes, and possible increase in the frequency of lung cancer.<sup>32</sup> Oral administration has been evaluated. However, there is a poor and variable absorption with this route,<sup>33</sup> at least for the cannabinoid formulations that have been investigated so far.

## Mechanism of IOP reduction

The mechanism of action of cannabinoids in the human eye is not fully understood. Until recently, the effect of cannabinoids on IOP was assumed to be mediated through the CNS. Studies involving unilateral topical application of cannabinoids<sup>34, 35</sup> showed a large difference between the treated and untreated eye, suggesting a localised action. The experiments of Liu *et al*<sup>36</sup> revealed evidence pointing in the same direction: bolus administration of  $\Delta^9$ -THC into the cerebral ventricles, as well as ventriculocisternal perfusion with  $\Delta^9$ -THC in rabbits, in contrast with intravenous administration, did not change the IOP. Thus, the main site of action of cannabinoids on IOP is not in the central nervous system.

Pharmacological and histological studies support the direct role of ocular CB<sub>1</sub> receptors in the IOP reduction induced by cannabinoids. Straiker *et al*<sup>11</sup> detected CB<sub>1</sub> receptors in ocular tissues of the human eye, including the ciliary epithelium, the trabecular meshwork, Schlemm's canal, ciliary muscle, ciliary body vessels, and retina. Porcella *et al*<sup>10</sup> found high levels of CB<sub>1</sub> mRNA in the ciliary body. The anatomical distribution of cannabinoid receptors suggests a possible influence of endogenous cannabinoids on trabecular and uveoscleral aqueous humour outflow and on aqueous humour production. In addition to the proved IOP lowering effect of CB<sub>1</sub> receptor agonists, Pate *et al*<sup>37</sup> could antagonise the IOP lowering effect of CP-55,940 (a synthetic CB<sub>1</sub> agonist) by pretreating the animals with SR 141716A (a CB<sub>1</sub> receptor antagonist). Similarly, Song *et al*<sup>38</sup> found that the IOP lowering effect of topical WIN-55,212-2 was significantly reduced by topically administered SR141716A.

Using the synthetic cannabinoid WIN-55,212-2, Chien *et al*<sup>39</sup> could demonstrate an 18% reduction in the aqueous humour production in monkeys but without significant change in the trabecular outflow facility. As this percentage appeared not sufficient to account for the total IOP lowering effect, other additional mechanisms were thought to be involved.

The IOP reducing effect does not seem to be related to a systemic reduction of arterial blood pressure.<sup>40</sup> However, a direct effect on the ciliary processes, and specifically a reduction in capillary pressure, leading to changes in aqueous humour dynamics, has been proposed.<sup>41</sup> Green *et al*<sup>42</sup> showed



that  $\Delta^9$ -THC decreased the secretion of ciliary processes and led to a dilatation of the ocular blood vessels through a possible  $\beta$  adrenergic action. In addition, Sugrue<sup>43</sup> indicated that cannabinoids may inhibit calcium influx through presynaptic channels and in this way reduce the noradrenaline release in the ciliary body, leading to a decrease in the production of aqueous humour. Porcella *et al*<sup>10</sup> proposed that cannabinoids might be acting as vasodilators on blood vessels of the anterior uvea, thus improving the aqueous humour uveoscleral outflow.

Green *et al*<sup>44, 45</sup> postulated that some cannabinoids may influence the IOP through a prostaglandin mediated mechanism. For example, topically applied AEA is hydrolysed to arachidonic acid, which is a COX pathway precursor of prostaglandins.<sup>46, 47</sup>

The topical application of the CB<sub>2</sub> receptor agonist JWH-133 used in in vivo experiments by Laine *et al*<sup>48</sup> did not have any effect on IOP compared to vehicle treatments, indicating that CB<sub>2</sub> receptor agonists may not be involved in the regulation of IOP.

### Topical application of cannabinoids

To minimise possible systemic adverse side effects and maximise the dose at the site of action, topical application would be the ideal form of administration. However, natural cannabinoid extracts as well as synthetic forms are highly lipophilic and have low aqueous solubility, creating practical difficulties for this mode of administration.

After instillation of an eye drop of any medication, loss of the instilled solution via the lacrimal drainage system and poor drug penetration results in only <5% of an applied dose reaching the intraocular tissues. The cornea is usually the major pathway for intraocular penetration of topical medications. The corneal epithelium is highly lipophilic and its penetration is a rate limiting step for lipophilic drugs. Aqueous solubility is another drug property important for efficacy of delivery, as the surface of the eye is constantly moistened by tear fluid. Additional factors affecting corneal absorption include the molecular size, charge, and degree of ionisation.<sup>49</sup>

Previous experiments with topical cannabinoid solutions involved the use of light mineral oil as a vehicle, but proved to be irritant to the human eye.<sup>50, 51</sup> Recently, different microemulsions and cyclodextrins (macrocylic oligosaccharides) have been shown to improve the corneal penetration of cannabinoids. These formulations successfully induced an unilateral IOP lowering effect.<sup>52–58</sup> Cyclodextrins have already been used efficiently by Porcella *et al*<sup>56</sup> to administer the synthetic cannabinoid WIN-55,212-2 topically to glaucoma patients.

### Neuroprotective and vascular actions of cannabinoids

In glaucoma, the final pathway leading to visual loss is the selective death of retinal ganglion cells through apoptosis. Apoptosis is initiated by axonal injury at the optic disc, either by compression and/or by ischaemia. In ischaemia, glutamate is released and activates NMDA receptors. NMDA receptor activation appears to be one of several pathways that result in apoptotic cell death. After activation of NMDA receptors there is an influx of calcium into the cells and free radicals are generated. Substances that prevent this cascade of events and inhibit the retinal ganglion cell death are currently under investigation.<sup>59</sup>

Recent studies have documented the neuroprotective properties of cannabinoids. There is evidence that  $\Delta^9$ -THC can inhibit glutamic acid release by increasing K<sup>+</sup> and decreasing Ca<sup>2+</sup> permeability and that the synthetic cannabinoid HU-211 can block glutamate (NMDA) receptors.<sup>8, 9, 18, 59–62</sup> These actions are mediated by presynaptic CB<sub>1</sub> receptors. Yoles *et al*, using a calibrated crush injury to adult

rat optic nerve (optic nerve axotomy), showed a beneficial effect of HU-211 on injury induced metabolic and electrophysiological deficits.<sup>63</sup> However, the optic nerve crush model may not resemble the mechanisms responsible for glaucomatous nerve damage.

Classic cannabinoids such as  $\Delta^9$ -THC, HU-211, and CBD have antioxidant properties that are not mediated by the CB<sub>1</sub> receptor. As a result, they can prevent neuronal death by scavenging toxic reactive oxygen species produced by overstimulation of receptors for the excitatory neurotransmitter, glutamic acid.<sup>7, 16–18, 64</sup>

Cannabinoids have vasorelaxant properties and so might be able to increase the ocular blood flow. The mediator endothelin-1, produced by vascular endothelial cells, has a significant role in the regulation of local circulation, producing vasoconstriction and being involved in the pathophysiological processes of ischaemic and haemorrhagic stroke, Raynaud's phenomenon, ischaemic heart disease and pulmonary arterial hypertension, among others.<sup>65</sup> The possible role of endothelin-1 in the pathogenesis of glaucoma has been suggested. For example, patients with open angle glaucoma may have an abnormal increase in plasma endothelin-1 in response to vasospastic stimuli.<sup>66, 67</sup> Mechoulam *et al*<sup>61</sup> could demonstrate that 2-arachidonoylglycerol, an endogenous cannabinoid, was able to reduce endothelin induced Ca<sup>2+</sup> mobilisation, inhibiting vasoconstriction. Thus, cannabinoids may have beneficial properties in ischaemia induced optic nerve damage.

### FUTURE DIRECTIONS

Cannabinoids have the potential of becoming a useful treatment for glaucoma, as they seem to have neuroprotective properties and effectively reduce intraocular pressure. However, several challenges need to be overcome, including the problems associated with unwanted systemic side effects (psychotropic, reduction in systemic blood pressure), possible tolerance, and the difficulty in formulating a stable and effective topical preparation. Some cannabinoids such as HU-211 and cannabidiol do not have psychotropic effects, while maintaining their IOP lowering action, so that further research on these compounds would be desirable. Tolerance may develop after repeated use of cannabinoids.<sup>30</sup> However, tolerance might be beneficial if it develops only or preferentially to unwanted side effects. There has been recent progress in the use of microemulsions and cyclodextrins to overcome the barriers in ocular penetration of topically applied cannabinoids.

Other possible applications of cannabinoids in ophthalmology could be explored. Age related macular degeneration (AMD) is the leading cause of blindness in the United Kingdom. Perhaps the potent antioxidant properties of the cannabinoids may be beneficial in AMD, offering a possible alternative to established antioxidant supplements.<sup>68</sup> Cannabinoids have been shown to inhibit angiogenesis, leading to a decrease in the expression of proangiogenic factors such as VEGF.<sup>69</sup> Evidence suggests that VEGF plays a major part in the development of choroidal neovascularisation in AMD, and clinical trials using anti-VEGF therapies are being conducted.<sup>70</sup> The CB<sub>2</sub> receptors are also under intense investigation for their possible immunomodulatory effects.<sup>71</sup> The anti-inflammatory properties of CB<sub>2</sub> receptor agonists might also prove to be of therapeutic relevance in different forms of inflammatory eye disease.

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