has yet investigated to what extent the genetic networks discussed in this paper are involved in regulating the expression of light-absorbing molecules in plants or bacteria.

2. Can you think of any animal outside these taxonomical groups? It is hard for most of us, and that is why it seems like every animal on Earth has eyes. Well, our truly eyeless relatives in Animalia would be the marine sponges, sea urchins, starfishes, jellyfishes and a whole lot of marine and land worms. Other than those, animals with no eyes were theoretically bound to have them but lost them sometime later in evolution.

3. A quick, harmless comment about nomenclature in Drosophila genetics. Like with all other model organisms, genes in Drosophila were first identified based on their mutations, and they would typically inherit a name related to the phenotype caused by such mutations. Thus, one of the first genes found to be involved in forming an eye in Drosophila was “ironically” named eyeless, because its mutated version was first pinpointed in flies that had no eyes. Later on, as mutations and phenotypes started accumulating and became subtler, Drosophila geneticists turned more sophisticated and creative, which leaves you with genes like grouch, capuccino, zucchini, stardust, torpedo, bag-of-marbles, egalitarian, pepper corn, hedgehog, decapentaplegic, armadillo, traffic jam, spaghetti squash and our all-time favorite cubitus interruptus.

References

Evaluating Non-Conventional Treatments for Glaucoma: A Review Article

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In the summer of 2001, the Canadian federal government amended the Narcotic Control Regulations to allow the Marijuana Medical Access Regulations to come into force. The new legislation allowed for the use of marijuana by patients suffering from serious illnesses in cases where it was expected to have clinical benefits that outweighed potential risks. Cannabis helps alleviate symptoms of nausea, vomiting, and loss of appetite leading to weight loss in patients suffering from severe chronic diseases.1

More recently, the Canadian government has proposed legislation to decriminalize the possession of small amounts of marijuana. Decriminalization would allow convicted offenders to receive a monetary fine rather than face the prospect of a criminal record and potential jail time. These recent proposed and accepted legislation changes for relaxing marijuana enforcement have helped rekindle discussion and research into medicinal applications of marijuana and cannabinoids (a family of biologically active molecules found in marijuana) in both the medical and lay press.

The first formal report of the use of cannabis as a medicine dates back nearly 5,000 years to China, where it was used as a treatment for malaria, constipation, joint pains, pain of childbirth, and, when mixed with wine, a surgical anaesthetic.2 Subsequent records exist of its use throughout Asia, the Middle East, Southern Africa and South America. It did not become a mainstream medicine in Canada, USA, and Britain until the 19th century and peaked in popularity during the mid to late 19th century.1

Towards the end of the 19th century, the role of cannabis as a prescribed medicine began a steep decline in popularity due to concerns about its unpredictable potency and response to oral administration, as well as its poor storage stability. Increasing enthusiasm for synthetic alternatives and American concerns about its use as a recreational substance were also important factors. Although the renowned physician Sir William Osler was still recommending marijuana for migraine sufferers as late as 1913, cannabis was finally outlawed in 1928 by the ratification of the 1925 Geneva Convention on the manufacture, sale and movement of dangerous drugs.1

Since that time, proponents have argued in favour of having cannabis reinstated as a viable medical treatment. Many lobby groups, for example, have advocated marijuana use for decades on behalf of chronic disease sufferers. Only the current social and political climate of acceptance and leniency towards marijuana use, however,
has allowed proponents of medical marijuana to be heard and supported by mainstream society. The recent proposed decriminalization of marijuana demonstrates society’s change in perception of marijuana as a dangerous drug to one of a more benign and potentially medically beneficial substance.

Although it has been accepted for restricted use in Canada to help alleviate constitutional symptoms brought on by chronic diseases, other potential medical applications for marijuana and cannabinoids do exist and have been studied and described in the medical literature.

While this article will focus mainly on the evidence surrounding the effectiveness of marijuana and cannabinoids in treating glaucoma, many other potential medical applications of the substance exist, with varying levels of evidence to support or refute its therapeutic qualities. These applications include alleviating symptoms of nausea, vomiting, loss of appetite with weight loss, and various types of pain (muscle, joint, bone, menstrual, labour, migraine and neuropathic) as well as treating insomnia, anxiety, depression, asthma, epilepsy (to prevent seizures), and multiple sclerosis.²,³

Glaucoma (we will only consider the “open-angle” type, which is the most common) is a painless and insidious eye disease caused by a failure of aqueous humour (a fluid inside the eye) outflow from the eye, leading to increased pressure inside the eye (intraocular pressure) and progressive loss of peripheral vision. If the condition is detected early enough and managed appropriately, severe vision loss and complete blindness can usually be prevented. Glaucoma is estimated to affect 70 million people worldwide, of which one tenth, or 7 million, are totally blind.⁴ A disproportionate number of those who have completely lost their vision live in third world nations where adequate medical therapies are severely lacking.

Diagnosis of glaucoma requires at least two of the following three clinical features: ocular hypertension (increased intraocular pressure), pathologic changes to the optic nerve at its site of insertion into the retina at the back of the eye (known as optic neuropathy or optic disc “cupping”), and progressive loss of peripheral vision (known as visual field loss).⁵

An abnormally high intraocular pressure (IOP) is generally accepted as the main factor in the development of the pathological optic nerve changes and peripheral visual field losses found in glaucoma. As a result, current treatment strategies to prevent or control glaucoma are based on lowering the IOP. A normal human intraocular pressure ranges from 10-21 mmHg with a mean of 15. Some eyes have an IOP above 21 with no glaucomatous changes while others acquire pathological changes despite having IOP values within the “normal” range. This underscores the importance of not diagnosing glaucoma based on IOP alone.⁶

Because glaucoma is a chronic condition without a cure, the development of new agents to lower IOP (ocular hypotensives) remains paramount in the ongoing fight to control the disease. Most drugs used for long-term glaucoma therapy are applied topically (eye drops) and are generally well tolerated.

Systemic side effects can occur, however, affecting the cardiovascular, pulmonary,
in the general glaucoma population.

Perez-Reyes et al\textsuperscript{10} were the first group to look at the effects of intravenous (IV) administration of various biologically active components of marijuana on IOP. Five different cannabinoids were tested on 12 non-glaucoma subjects in a randomized, placebo-controlled, double-blind study. The authors found that D9THC, delta-8-THC and 11-hydroxy-THC did produce significant short-term reductions in IOP while 8-beta-hydroxy-THC and cannabidiol were less effective. Effects on blood pressure and heart rate were not described.

A topical (eye drop) form of D9THC was also tested for IOP-lowering effects by Merritt et al\textsuperscript{11} who tested topical D9THC on eight glaucoma subjects and found a significant dose-related reduction in IOP. They also reported no psychoactive effects but did find subjects to develop mild systemic hypotension. Roth and Green,\textsuperscript{12} on the other hand, reported topical D9THC to have no effect on IOP but to cause transient eye burning, tearing and conjunctival redness. Jones et al\textsuperscript{13} tested an oral formulation of D9THC on 13 subjects without glaucoma in a double-blind, placebo-controlled study and found that although the drug did produce significant IOP-lowering effects, any results tended to tolerate out by 10 days of regular dosing. Furthermore, abrupt withdrawal of the THC produced rebound increases in IOP above baseline.

At this stage, the exact mechanism of action of cannabinoid compounds in marijuana remained unknown. Because of the related psychoactive effects, researchers initially believed that the IOP-lowering effect was mediated through the central nervous system (CNS). This belief changed, however, when Liu and Dacus\textsuperscript{14} demonstrated that administration of IV D9THC decreased IOP in rabbit eyes while cerebral administration of the compound had no IOP effect, indicating a probable non-CNS mechanism to be responsible for IOP reduction.

By the late 1980s and into the mid 1990s, marijuana and its cannabinoid components were generally considered to be of limited potential as future therapeutic agents in the treatment of glaucoma. Too many questions existed regarding systemic side effects, short duration of action with subsequent rebound effect, and psychoactive effects to keep them at the forefront of clinical research interest. Research was maintained mostly for the insight gleaned into the physiology of IOP control.

Recent research, however, has shone new light on the potential for cannabinoids to be effective IOP-lowering agents. In the late 1980s, the central cannabinoid (CB1) receptor, to which many cannabinoids found in marijuana bind, was cloned and characterized.\textsuperscript{15,16} Speculation about the role of this receptor in cannabinoid-mediated IOP reduction was fuelled by reports in the mid 1990s of a series of synthetic cannabinoid analogues that showed significant IOP-lowering effects when applied topically to rabbits with normotensive (normal IOP) eyes.

Hodges et al\textsuperscript{20} provided evidence against the theory that linked the CB1 receptor to cannabinoid-mediated IOP reduction. They found that WIN55212-2, a synthetic cannabinoid known to have strong affinity for the CB1 receptor, did not produce any IOP-lowering effects when given systemically to normotensive rabbits. A well-designed experiment by Pace et al\textsuperscript{21} swung the pendulum back in favour of the IOP reduction-CB1 receptor relationship when it was demonstrated that normotensive rabbits pretreated with a subcutaneous injection of a known CB1 receptor antagonist showed no IOP reduction following topical administration of two synthetic cannabinoids. The same two cannabinoids, meanwhile, when applied topically to rabbits not pretreated with the CB1 receptor antagonist, caused a significant IOP reduction.

The findings of Hodges et al\textsuperscript{20} that opposed the putative theory of cannabinoid/CB1 receptor-induced IOP reduction were most likely due to the use of systemic cannabinoid administration in the study. Other studies that seemed to support the proposed link all used topically administered cannabinoids. Furthermore, a study carried out three years later did show an IOP-lowering effect using topically applied WIN55212-2, the same cannabinoid used in the study by Hodges et al, in normotensive rabbits.\textsuperscript{22}

How a cannabinoid applied topically and systemically can have such markedly different effects on IOP was still undetermined. Between 1998 and 2000, Pocella et al\textsuperscript{25} provided breakthrough evidence into elucidating the exact mechanism by which cannabinoids mediate IOP reduction. They found that high levels of CB1 receptor mRNA and protein exist in the rat\textsuperscript{23} and human\textsuperscript{24} ciliary body. The ciliary body is the ocular structure partly responsible for both the production and drainage of aqueous humour inside the eye. The presence of large amounts of CB1 receptor in the ciliary body and the variability in IOP effect between topical and systemic cannabinoid administrations support a direct role for the CB1 receptor present in the ciliary body in the control of IOP.

The discovery of ciliary body cannabinoid receptors and its implication towards a possible explanation for the ocular hypotension mediated by topical cannabinoids has stimulated a new phase of ophthalmic cannabinoid research. Pocella et al\textsuperscript{25} studied the clinical effects of a topical formulation of the synthetic cannabinoid WIN55212-2 in eight human glaucoma subjects resistant to conventional medical therapies. Although the study was neither placebo controlled nor randomized, the results did show a statistically significant IOP reduction of up to 31%, with a peak reduction at 60 minutes following administration. The authors commented that the exact nature of IOP reduction, whether caused by decreased aqueous humour production or increased aqueous humour outflow from the eye, would require further investigation.

A non-psychoactive synthetic cannabinoid, HU-211, was recently developed and has been studied for its IOP-lowering effects in normotensive rabbits. As expected, topical HU-211 produced an IOP-lowering effect that was first evident at 1.5 hours post-dose and persisted for six hours.\textsuperscript{26} Interestingly, IV administration of HU-211 also produced a drop in IOP, with a maximal IOP reduction at four hours post-administration.\textsuperscript{27} Furthermore, systemic use of this cannabinoid showed no effects on blood pressure, heart rate or pupil dilation. The authors also determined that the rate of aqueous humour inflow was unchanged by the drug, lending support to the theory of increased aqueous humour outflow as the main mechanism of action.

The path that has led researchers from initially testing inhaled marijuana as an anti-glaucoma agent to current attempts at elucidating the mechanisms of cannabinoid-
mediated lowering of the IOP has been long and arduous, and is far from complete. Recent research into cannabinoid function, however, gives cause for optimism. Efforts aimed at developing effective IOP-lowering cannabinoid agents are beginning to show promise. Animal testing with the synthetic cannabinoid HU-211 has yielded results that have thus far avoided the clinical problems caused by the natural cannabinoids found in marijuana. This newer synthetic agent has shown a longer duration of action, fewer systemic side effects, and none of the psychotropic effects commonly associated with marijuana. Future human study of this and other safe, potentially effective cannabinoid agents is warranted, with the ultimate goal of producing dependable and well-tolerated medications with strong IOP-lowering effects.

These drug development initiatives will hopefully provide ophthalmologists with a greater range of medications to choose from in order to help prevent vision loss caused by glaucoma.

REFERENCES

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