Marihuana and the eye

The first report of a decrease in intraocular pressure following smoking of marihuana was received with a fair amount of skepticism, mirth, and bad publicity in the press, such as articles informing the public of a new “cure” for glaucoma. Now that the smoke has cleared, it is time to evaluate the effects of marihuana on the eye and make an objective assessment of the potential therapeutic value of this drug (rather, a group of drugs) in ophthalmology, while putting aside the moral and ethical discussion of the use of marihuana in society as a drug of abuse.

Many questions are immediately forthcoming. Does the drug really act to consistently reduce intraocular pressure? If so, how does it work? What are the side effects? Can one use a topical drop? Is there a compound which is active as regards intraocular pressure without producing undesired systemic and central effects? Some of these questions can be answered at this time while others await more detailed examination.

It is now well documented that marihuana, or its primary active ingredient delta-9-tetrahydrocannabinol ($\Delta^9$-THC), when given to rabbit or man by several routes, reduces intraocular pressure. The group at UCLA, continuing their initial efforts, find that chronic smoking of marihuana by inpatients (average of 15 “joints” per day for 94 days) always causes an intraocular pressure fall which lasts for four to five hours even after one “joint.” The intraocular pressure decrease appears to be unrelated to the total number of cigarettes smoked, suggesting that the plasma dose of THC reached after one cigarette is sufficient to evoke the maximal response. No immediate or cumulative effects were observed on any measure of ocular status, including visual fields, visual acuity, tomography, slit lamp biomicroscopy, electroretinogram (ERG), and the appearance of the fundus. Only ocular pulse pressure and tear secretion decreased after THC, both by statistically significant amounts, together with a slight pupillary constriction. In patients with ocular hypertension or glaucoma, seven of 11 patients showed an intraocular pressure fall of 30 per cent.

Another study, however, also utilizing confined patients, revealed that a tolerance developed to the oral administration of $\Delta^9$-THC; the dose level, however, was much higher than that used in the study where the marihuana was smoked. The intraocular pressure showed an initial fall after oral use and returned to baseline as tolerance developed. Further smoking of marihuana in this patient group failed to cause a fall in intraocular pressure. Prob-
lems arise in the interpretation of this data, however, since oral administration causes both longer lasting and higher plasma levels of THC than after smoking, thus the findings may vary with sustained high or low plasma concentrations. One study on long-term (one year) marihuana smokers in Costa Rica has shown that there are no discernible effects on intraocular pressure or color vision, compared to a control group of non-users. A more detailed study, examining many more ocular parameters is currently in progress. One-time examination of marihuana users in Europe revealed changes in visual acuity, marked blepharospasm, and a degree of photophobia associated with long-term use, as well as a prolonged fall in intraocular pressure as long as three weeks after the last admitted use of the drug. This latter study suffers from the problem that the patients may have been multiple drug users and, since they were not inpatients, also faulty reporting on the part of the users who often exaggerate the time since last drug use. The use of a nonpsychotrophic dose in open-angle glaucoma is being investigated currently. Single intravenous infusions of Δ9-THC and several derivatives by several investigators also reveal substantial intraocular pressure falls.

The reduction in ocular pressure pulse seen in man, together with studies in rabbit which show an increased blood-aqueous barrier permeability (measured directly in vitro and by increased aqueous protein in vivo) concurrent with the intraocular pressure fall, suggest that the action of the cannabinoids is a vasoconstriction of the afferent vessels of the ciliary body causing a pressure fall in the capillaries. This effect occurs concurrently and paradoxically with an engorgement of conjunctival vessels by a mechanism which is not yet understood. Whether the inhibition of prostaglandin synthesis by Δ9-THC is of importance in the nonstimulated eye remains to be determined; certainly THC inhibits the formation of prostaglandin from arachidonic acid when the latter is given in large quantities to the eye.

Obviously, smoking and intravenous infusion are neither feasible nor desirable as a means of treatment for the reduction of intraocular pressure in man. The most advantageous route is topical administration but, thus far, tests have only been made in the rabbit using Δ9-THC and several derivatives. The UCLA group using Δ9-THC in normal eyes and Mechoulam and Dikstein in Jerusalem using cannabinol acetate in buphthalmic eyes, find a substantial reduction in intraocular pressure after use. Work at the Medical College of Georgia, using Δ9-THC and many derivatives applied to the eye in sesame oil, has demonstrated the relative potency of these compounds and, currently, dose-response curves for the active drugs are being established.

Some compounds which reduce intraocular pressure when applied topically to the rabbit eye, such as cannabinol, 8α- and 8β-11-diol Δ9-THC and Δ10-THC are known to have little or no central effects and, as such, are high in priority for study, since if there is systemic absorption (as occurs in the rabbit at the presently used dose levels, and occurs in man with other drugs) fewer side effects are desirable and necessary. The vehicle of choice for the drug as a topical agent is of great importance since it must satisfy the requirements of THC solubility, shelf stability, and release of the drug into the eye. An intensive investigation using a multidisciplinary approach would answer many unresolved questions concerning the potential use of these agents in ophthalmology. It is immediately obvious that there is a great need for further study of these compounds, and the ophthalmologist in clinical practice and research should not only be aware of the clinical effects of these drugs in man but also of their potential therapeutic use.

Preclinical and clinical studies indicate, thus far, that the intraocular pressure fall is as good as or better than most agents
currently available. The decrease in intraocular pressure probably represents one of the most potentially valuable therapeutic uses of these compounds. If clinical trials indicate no long-term effects, either local or systemic, following the use of a topically applied cannabinoid it is most likely that such an agent will be made available for clinical use by the ophthalmologist. It would be unfortunate if the possible importance of these chemically unique drugs in ophthalmology were to be clouded by the notoriety which the drug has achieved in society.

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REFERENCES

Cyclic nucleotide metabolism in the retina

Critical metabolic links in the understanding of a variety of intracellular metabolic events have been developed in the role played by the cyclic nucleotide compounds adenosine 3'-5' cyclic phosphate (cAMP) and guanosine 3'-5' cyclic phosphate (cGMP). All mammalian systems appear to harbor these biochemical messengers which are formed by a simple one-step dephosphorylation and cyclization from the parent compounds adenosine triphosphate (ATP) and guanosine triphosphate (GTP) by the appropriate nucleotidyl cyclase. Knowledge of the universal distribution and broad metabolic role which these biocompounds play has rapidly accumulated and now includes a body of provocative data about the role they might play in the metabolism of the mammalian retina. In particular is the evidence for the link they may provide in the transmission of the message from light stimulation of the retina to the electrical signal detected by the central nervous system.

The first detection of the existence of these compounds was in the rat retina, in which the presence of remarkably high concentrations of intermediates of the guanylate series proved to be in distinct contrast to other neural tissues. Manipulation of levels of the cyclic nucleotides was readily accomplished in other tissues.