Chapter 3

OCULAR EFFECTS OF CANNABINOIDS

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I. INTRODUCTION

In considering the ocular actions of the cannabinoids, the principal effect with which we are concerned is the ability of marijuana and its constituents, especially Δ^9-tetrahydrocannabinol (THC), to lower intraocular pressure. It is for this effect that the cannabinoids have been utilized in the treatment of glaucoma. In this chapter, we will review the pressure-lowering effects of the compounds, discuss the problems associated with the administration of these chemicals for that purpose, and assess their potential therapeutic value. In addition, we will examine other effects that the cannabinoids have on the eye. In order to accomplish these aims, the chapter will be divided into four sections: the first will consider the anatomy and physiology of the eye as it relates to glaucoma and the pharmacological therapy for the disease. Some factors important in the use of drugs to treat this condition (e.g., pharmacokinetics) will be included. The second section will present information about the different types of glaucoma. In the third section, we will deal with the cannabinoids, both naturally occurring and synthetic, in the treatment of glaucoma and ocular hypertension. This discussion will be preceded by a brief description of the current pharmacotherapy for these conditions. The final section of the chapter will discuss other ocular effects that are known to result from the use of cannabinoids.

II. ANATOMY, PHYSIOLOGY, AND PHARMACOKINETICS OF THE EYE

In order to understand the ocular effects of pharmacological agents, some knowledge of the anatomy and physiology of the eye is essential. Consequently, those aspects of the anatomy and physiology of the human eye that are of particular relevance to the pharmacotherapy of glaucoma and related conditions will be covered briefly.

The eyeball, or globe, consists of three separate concentric layers. The outermost layer is the sclera, the middle layer, the uvea, and the innermost layer, the retina. These layers are diagrammed in Figure 1.

The sclera serves for protection of the eye and consists of an opaque layer covering about five sixths of the surface of the globe and a central transparent portion, the cornea. For ease of presentation, the canal of Schlemm will be considered part of the scleral layer. It is a sinus which lies within the deeper layers of the sclera at the limbus. The wall of the canal consists of endothelium and a basement membrane and is separated from the anterior chamber of the eye by the trabecular meshwork. From the viewpoint of understanding the pharmacotherapy of glaucoma, these structures are of prime importance since the aqueous humor drains through the trabecular meshwork into the canal of Schlemm. More will be said about these structures in subsequent parts of this chapter.

The uvea is the middle layer and consists of the choroid, ciliary body, and iris. The choroid is a vascular layer supplying blood to the retina; the ciliary body functions both to alter the shape of the lens in accommodation and to secrete aqueous humor; the iris surrounds the pupil, the opening that controls the amount of light entering the eye. Pupillary size is regulated by the sphincter pupillae (parasympathetic) and the dilator pupillae (sympathetic).

The innermost layer is the retina, the light-sensitive structure of the eye responsible for transmission of visual impulses by way of the optic nerve. Miosis occurs when increased light reaches the retina, resulting in increased impulses to the oculomotor nerve through the optic nerve. Elevated parasympathetic activity then causes pupillary constriction by means of contraction of the sphincter and relaxation of the dilator. In the presence of decreased light, the opposite occurs.

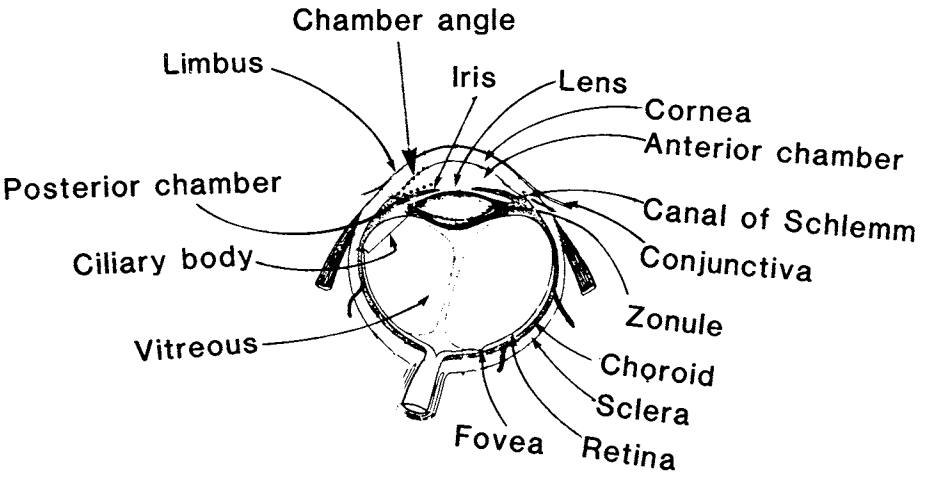


FIGURE 1. Structure of the eye.

The eye contains three chambers: anterior, posterior, and vitreous. The anterior chamber lies between the cornea and the anterior surface of the lens and iris. Peripherally, it is bounded by the anterior chamber angle. The smaller posterior chamber lies between the iris and the vitreous. The ciliary processes produce the aqueous humor and secrete it into the posterior chamber from where it flows through the pupil into the anterior chamber. Posterior to the lens, and occupying about four fifths of the globe, is the vitreous chamber or cavity. It is filled with the vitreous humor, a transparent, jelly-like substance.

With the above brief description of the anatomy in mind, let us see how the physiological functions and biochemical composition of these structures affect the pharmacotherapy of glaucoma and the ocular actions of drugs. When a drug is administered systemically, high concentrations can reach the eyelids and orbital structures (e.g., retina or optic nerve) because of their rich vascularization. However, the blood-aqueous barrier impedes access of the drug into the aqueous of the anterior chamber. Two routes are available for the drug: through the epithelium of the ciliary body and by diffusion from the iris capillaries. Even if one could be assured that systemically administered drugs would exert their desired effects on the eye, however, such routes of administration would not be desirable in most cases. One would have to accept general systemic activity of drugs in order to get ocular effects. To obviate that problem, the preferable method of administering pharmacological agents is topically to the eye. As simple as such a technique seems, it is fraught with difficulties because of the chemical composition of the eyeball.

Although a drug administered into the conjunctival sac can also enter the eye by way of the conjunctiva, the principal route is across the cornea. The cornea presents three major barriers to a drug. The first is the anterior epithelial layer, a lipoidal structure. Passage through this layer is enhanced by lipid solubility and a nonpolar, nonionized molecule. Once through the epithelium, the compound must cross the stroma, a structure which favors passage of hydrophilic, ionized, polar compounds. The third barrier is the endothelial layer, a structure which again requires lipophilicity. Thus, there is a lipid, a water, and another lipid barrier. It has been estimated that the lipid content of the epithelium and the endothelium is about 100 times greater than that of the corneal stroma.[1] In addition to lipid solubility, important determinants of passage are molecular weight (with the maximum being about 70,000),[2] binding to proteins (since only unbound drug can diffuse) and, possibly, active transport. Medications that readily

enter the eye after topical application must have the ability to exist in equilibrium in solution in both ionized and nonionized forms. Although the barriers could be circumvented by injecting a drug directly into the orbit, this would certainly not be a practical way to treat glaucoma medically.

Intraocular concentrations are determined not only by the entrance of the drug, but by the rate of its removal via diffusion into blood vessels and by removal via the aqueous humor into the canal of Schlemm. As in all tissues of the body, the presence of specific receptors for the drug can result in high concentrations in particular areas where the drug is bound to the receptor. Among the factors to be considered in predicting how much of a drug will penetrate the eye are the extent to which the drop is diluted by the tears in the conjunctival sac and the rapidity with which the tears wash it out. Furthermore, only a small amount of fluid can be accommodated by the conjunctival sac and, consequently, the excess spills out. Absorption into the general circulation can occur since the drug can enter the nasolacrimal passages. Ointments are sometimes used to enhance the penetration of drugs, although eye drops are the preferred method for topical drug administration. Maurice and Mishima[2] have proposed a two-compartment model open system of conventional pharmacokinetics to analyze the exchanges occurring within the eye after the topical administration of a drug. The assumptions are that (1) loss of drug to the tears from the cornea is negligible; (2) entry into the aqueous humor from the tears other than through the cornea is negligible; (3) exchanges between the cornea and the blood at the limbus are unimportant; and (4) exchanges of the aqueous humor with the posterior reservoir are negligible. They present evidence showing that the model holds up reasonably well.

Obviously, a variety of pathological conditions (e.g., damage to the cornea or inflammation) will affect the kinetics of drug penetration. The prime interest in this chapter, however, is glaucoma and, in this condition, there appears to be no change in the flow rate or in the intraocular barriers.

III. GLAUCOMA

In 1982, the Institute of Medicine stated that glaucoma was the leading cause of blindness in the U.S.[3] Over two million people over the age of 35 in this country alone are afflicted with glaucoma and it has been estimated that 300,000 new cases are diagnosed each year. It is a condition which is generally characterized by an increase in intraocular pressure (IOP) that progressively impairs vision and may lead to absolute blindness. Glaucoma is not a single, discrete disease entity. Rather, there are many forms of the disease with different causes, different clinical courses, and requiring different therapies. It is generally age related, being most common in the elderly. Detection is usually at routine physical or eye examinations involving IOP measurement. Just as there are individuals who have high IOP but do not develop glaucoma, however, there are others with normal IOP readings who do develop the condition. These latter groups are atypical of the clinical picture. In addition to elevated IOP, loss of visual field and excavation of the optic disc are other characteristics of the disease. Although there are several classifications that can be used for the glaucomas, they are commonly divided into open- and closed-angle types. These types are then subdivided further into primary (unknown etiology) and secondary (cause is known). Acute and chronic forms of each type occur. Congenital glaucoma is often considered a separate category and includes both open- and closed-angle types. The key feature in the development of any of the glaucomas is some interference in the balance between the formation of the aqueous humor and its outflow. The problem is usually the result of some obstruction of the outflow which then leads to an increase in IOP. In general, IOP readings above 21 mmHg indicate the need for further studies (normal range is 12

to 21 mmHg). If other signs of glaucoma are absent, the condition is referred to as ocular hypertension. Such patients may or may not develop glaucoma, but are at higher risk.

At this point, it might be well to expand somewhat the discussion of the aqueous humor. It is a clear fluid similar to plasma but with much less protein. The chemistry of the aqueous may be found in numerous texts, notably a recent one edited by Davson.[4] As mentioned previously, the aqueous is formed by the ciliary processes with the aid of the enzyme carbonic anhydrase, and enters the posterior chamber. It then flows around the lens and through the pupil into the anterior chamber. Aqueous leaves the eye at the anterior chamber angle via two pathways: (1) the conventional (trabecular) route through the trabecular meshwork, canal of Schlemm, and then into the collector channels, aqueous veins, and general venous circulation; and (2) the unconventional or uveoscleral route across the iris and anterior face of the ciliary muscle, through connective tissue into the suprachoroidal space and then out the sclera. Although the exact percentage seems to vary from species to species, the trabecular route handles the majority of the drainage. The IOP is a reflection of the balance between inflow and outflow. A more detailed discussion of these issues can be found in a chapter by Kaufman et al.[5]

A. Primary Open-Angle Glaucoma

Primary open-angle glaucoma, also referred to as chronic simple glaucoma, is the most common form of glaucoma. Although the cause of this type is not definitely known, it is generally believed to result from an obstruction to the outflow of the aqueous humor somewhere in the trabecular meshwork, perhaps in the cribriform region adjacent to the inner wall of the canal of Schlemm. It is characterized by a gradual increase in IOP with almost a complete absence of other signs and, if not treated, leads to blindness. This type tends to occur after the age of 30 or 35, occurs more often in myopic individuals, and is almost always bilateral. Heredity plays an important role and it is believed that there is a multifactorial, or polygenic, inheritance. Diabetes mellitus is often a predisposing factor, although the reason for this relationship is not known.

B. Secondary Open-Angle Glaucoma

Secondary open-angle glaucoma can have a number of different causes. Although the defect in this type also lies in the outflow of the aqueous humor, such diverse conditions as anterior uveitis, intraocular tumors, enlarged cataracts, central retinal vein occlusion, intraocular hemorrhage, and trauma to the eye may be responsible for the interference with the outflow. Loss of pigment from the iris and subsequent deposition of the pigment in the trabecular meshwork may be due to an inborn defect and can also obstruct aqueous outflow. In exfoliation syndrome, an amyloid-like material is exfoliated from the surface of the lens by the action of the pupil and is eventually deposited in the trabecular meshwork. Corticosteroid therapy, either topical or systemic, may lead to an increase in IOP in a certain proportion of patients; the condition is usually reversible when treatment with the drugs is discontinued. Other conditions may also result in glaucoma; the interested reader can consult any standard text in the field.

C. Primary Closed-Angle Glaucoma

Primary closed-angle glaucoma is also known as angle-closure glaucoma, narrow-angle glaucoma, and uncompensated glaucoma. It occurs much more frequently in females than in males. The basic defect lies in the anatomy of the eye — there is a shallow anterior chamber and a smaller-than-usual corneal diameter. As a result, the

iris is located close to the trabecular meshwork and the lens is close to the cornea, becoming even closer with the normal increase in the size of the lens that occurs with aging. The eye is hyperopic. Together, these structural abnormalities lead to impaired flow of aqueous humor through the pupil, causing the aqueous to accumulate in the posterior chamber. The resulting increase in pressure in the posterior chamber leads to a ballooning out of the peripheral iris with a resultant decrease in the chamber angle. Dilation of the pupil causes the iris to become thicker, further diminishing drainage of the aqueous. As might be surmised, there is a strong hereditary component to primary angle-closure glaucoma. Intermittent attacks of acute angle-closure glaucoma may occur and may represent an intermediary phase to chronic angle-closure glaucoma. An acute attack is an ophthalmologic emergency and, if not treated quickly, may lead to severe loss of visual field and blindness. Attacks may be brought on by situations which result in a dilated pupil (e.g., mydriatic drugs, a darkened room, or emotional stress).

D. Secondary Closed-Angle Glaucoma

As was the case with secondary open-angle glaucoma, secondary closed-angle glaucoma can result from a variety of causes which prevent the aqueous humor from penetrating the trabecular meshwork. Included in these causes are pupillary block, postoperative complications from ocular surgery, inflammatory processes, intraocular tumors, and vascular problems.

E. Congenital Glaucoma

The final category of the glaucomas to be mentioned in this chapter is congenital glaucoma. It may be divided into the usual primary and secondary types. Congenital glaucoma is also referred to as buphthalmos, infantile glaucoma, and hydrophthalmos. It occurs in infants and children and is sometimes related to hereditary factors. The primary type is quite rare and is due to a congenital defect of the anterior chamber angle. The outflow of the aqueous is obstructed, resulting in a chronic increase in IOP which, in turn, leads to an enlargement of the globe. There is a thinning of the cornea and the pupil becomes large and fixed. If allowed to continue, the condition leads to damage to the optic nerve and blindness. Although there is often a category of secondary congenital glaucoma, the conditions causing it are usually similar to those causing secondary forms of glaucoma in the adult, the distinguishing feature being the age of the patient.

IV. THE TREATMENT OF GLAUCOMA AND OCULAR HYPERTENSION

A. General Considerations

In order to properly consider the role of cannabinoids in the treatment of glaucoma, a brief survey of the current medical therapies for this condition is necessary. More complete discussions, as well as numerous references, may be found in such texts as those by O'Connor Davies,[6] Ellis,[7] Havener,[1] Shields,[8] Trevor-Roper and Curran,[9] the book edited by Sears,[10] and in a review by Razdan and Howes.[11] In general, secondary glaucomas are best treated by means that try to correct the underlying problems. Such treatments would include discontinuation of the drug therapy which resulted in the increase in IOP, surgical management of traumatic injuries, and pharmacotherapy of infections. In addition, certain types of glaucoma, such as acute angle-closure and congenital, often require surgical intervention. In such cases, pharmacotherapy is only a temporary measure. In cases where medical management of glaucoma is the therapy of choice, a number of different drug classes may be employed. Such drugs include parasympathomimetics, adrenergic agonists and antagonists, carbonic anhydrase in-

hibitors, and agents administered for their osmotic effects. The primary therapeutic use of the drugs is either to increase outflow of the aqueous humor or to reduce production of the humor.

B. Standard Pharmacotherapy

The principal drugs that have been used for many years are the parasympathomimetics, agents that produce both a miosis and an increase in the outflow of the aqueous humor from the anterior chamber. Pilocarpine may be the most commonly used agent in this class and is administered in the form of eye drops two or three times a day. Only a portion of the pilocarpine gets through the cornea into the anterior chamber. It is effective in open-angle glaucoma because it facilitates the passage of the aqueous through the drainage angle, probably by stimulation of ciliary muscle contraction, which alters the configuration of the trabecular meshwork and the canal of Schlemm. However, it decreases uveoscleral flow. Since trabecular flow is more important in humans, the net result is an increased outflow and a decrease in the IOP. Whether or not there is a change in the aqueous formation is still undetermined. The miotic effect of pilocarpine is useful primarily in closed-angle glaucoma. Unfortunately, even in cases where it is effective, tolerance develops and the drug must be discontinued for a period of time until responsiveness to the drug returns. It must also be realized that there is a progressive deterioration of the trabecular meshwork in glaucoma, and what appears to be development of tolerance to drugs may sometimes be partically explainable in terms of the progressive nature of the disease. Systemic effects may be seen and these include typical muscarinic parasympathetic actions. Ocular side effects, including ciliary muscle spasm, may occur. Cholinesterase inhibitors can also be used and both reversible (e.g., physostigmine) and irreversible, long-acting inhibitors such as isoflurophate (DFP) have efficacy. Although each type has advantages and disadvantages, side effects with the latter are generally more numerous, more severe, and longer-lasting than with pilocarpine. As a general rule, combinations of parasympathetic drugs are not recommended since they do not seem to add to the IOP-lowering action of pilocarpine and may actually interfere with it.

As incongruous as it may seem, both adrenergic agonists and antagonists can lower IOP. It appears that alpha$_1$ receptors mediate increases in trabecular outflow, while the beta$_2$ receptors mediate changes in flow via reduction in inflow of the aqueous humor by the ciliary epithelium.[12] Rapid development of tolerance is a limiting factor in the use of beta adrenergic agonists. In addition, the IOP-lowering effect is modest, and side effects (e.g., irritation on instillation, adrenochrome deposits in the conjunctiva, or reactive conjunctival hyperemia) may pose problems. Epinephrine seems to exert its antiglaucoma actions by stimulation of both alpha and beta receptors. Since its effects are small, it is usually administered in combination with a parasympathomimetic agent. A major advance in the use of agents acting on the sympathetic nervous system to treat glaucoma came with the introduction of timolol, a nonselective antagonist at both beta$_1$ and beta$_2$ receptors. (In addition to information contained in the references above, the reader can also consult Chiou[13] and Zimmerman et al.[14]) The actions of timolol on IOP were achieved with far fewer problems than those accompanying the use of earlier beta blockers such as propranolol. Timolol lowers IOP by reducing the rate of formation of the aqueous humor and the effects last for at least 12 hr. Although the mechanism for its action is not completely known, it appears that beta blockade is only part of the story, perhaps even the smallest factor involved. Moreover, the IOP-lowering effect is achieved without significant changes in pupil size, visual acuity, or accomodation. The amount that IOP is lowered by timolol is equivalent to that seen with pilocarpine. It may be used with agents such as pilocarpine and carbonic anhydrase inhibitors to get additive effects. As is true with most other

agents administered to the eye, systemic absorption can lead to undesirable effects characteristic of the actions of the particular class of drugs. Adverse effects also occur in the eye (although they are quite infrequent) and include pain on instillation, superficial punctate keratitis, and allergic blepharoconjunctivitis. Tolerance to the IOP-lowering action has been reported, but it is too early to determine its incidence. Other beta blockers are also being tried at the present time. It should perhaps be mentioned at this point that studies with beta adrenergic agents indicate that coupling of this receptor to adenylate cyclase is involved in the IOP-lowering effects of these drugs. A relatively new agent, forskolin, seems to interact directly with the catalytic unit of adenylate cyclase in the ciliary epithelium of the eye and lowers IOP without interaction with the cell surface receptor.[12] Such a direct action, it is hoped, will prevent the development of tolerance. Mention should also be made of clonidine, an alpha$_2$ agonist, which has shown promise in lowering IOP.

Carbonic anhydrase inhibitors are the only systemically administered drugs used to treat glaucoma chronically. Although several agents of this class are in use at the present time, the prototype drug is acetazolamide (Diamox). Since the secretion of aqueous humor depends partially on the formation of bicarbonate ion from carbon dioxide, inhibition of carbonic anhydrase (which catalyzes the reaction) results in a drop in IOP due to a decrease in formation of the aqueous humor which may amount to 50 or 60%. There appears to be no change in outflow. Drugs in this class are administered orally and are effective, but side effects are numerous and include gastrointestinal upset, serum electrolyte imbalances, and elevated blood uric acid. They are used principally as supplementary therapy.

For short-term emergency situations, such as acute angle-closure glaucoma, drugs referred to as hyperosmotic agents may be administered systemically. They lower IOP by creating an osmotic gradient in which blood is hypertonic to the intraocular fluids, thus reducing vitreous volume. Drugs in this class include some that are orally administered, such as glycerol, and some that are given intravenously, such as mannitol or urea. The drugs have limited usefulness and cause numerous undesirable effects.

At this point, it might be well to summarize the pharmacotherapy of the glaucomas. An important point to remember is that the cause of secondary glaucoma is generally known and the treatment should be directed at correcting the underlying cause whenever feasible. For chronic open-angle glaucoma, there are a variety of agents, primarily pilocarpine and timolol. In aphakic eyes (congenital absence of the lens), the irreversible cholinesterase inhibitors are used. Epinephrine is sometimes prescribed in conjunction with pilocarpine. For acute angle-closure glaucoma, hyperosmotic agents and carbonic anhydrase inhibitors are often given. The miotics are also quite useful. The miotics, alone or in combination with timolol, are useful in the treatment of chronic angle-closure glaucoma. Despite the efficacy and relatively low incidence of serious side effects noted with some of the agents discussed above, none are ideal. All possess drawbacks such as unwanted effects or development of tolerance. It is because of the need for better antiglaucoma agents that interest has been shown in the cannabinoids.

C. The Cannabinoids

1. Marijuana and Δ^9-THC

The interest in cannabinoids as possible antiglaucoma agents stems from observations of the ability of marijuana and its major constituent, Δ^9-tetrahydrocannabinol (Δ^9-THC), to reduce IOP. Probably the first report of this action appeared in 1971 a letter to the editor of the *Journal of the American Medical Association*[15] in which a table presented data on eleven subjects, nine of whom demonstrated a drop in IOP, ranging from 16 to 45%, after smoking 2 g of marijuana. Shapiro[16] reported on a group of 350 habitual users, all of whom had low IOP, averaging 10 to 12 mmHg. A

study by Flom et al.[17] cast some doubt on whether the reduction of IOP was a direct effect of the drug or rather a consequence of the relaxed state induced in the subject. In their study, 15 young adult males who were experienced in smoking marijuana were given cigarettes containing 12 mg of Δ⁹-THC. Moderate to light users showed the greatest drop in pressure while heavy users, who experienced little of the "high", showed only a small, if any, decrease in IOP. A subsequent study on a group of ten young adult males who used marijuana, however, found a lowering of IOP concomitant with an increase in the anxiety state after approximately 1.5 or 3.0 mg of Δ⁹-THC given intravenously.[18] In both studies, there was large variability in response among subjects, with the peak effect usually occurring 60 to 90 min after drug administration. Reductions in IOP induced by cannabinoids have been reported in groups of volunteers who are free of ocular problems,[19,20] as well as in patients with ocular hypertension or glaucoma.[19,21] The decrease generally ranged from about 20 to 40% and lasted at least 4 hr. In some subjects, the fall in IOP was accompanied by cardiovascular and/or psychological effects. For example, tachycardia, decreased blood pressure, and postural hypotension were noted. Another study[22] found that in a group of 17 patients with heterogeneous glaucomas who were otherwise healthy and who were neither cigarette nor marijuana smokers, 5 or 10 mg of Δ⁹-THC given orally in gelatin capsules caused no significant decrease in IOP. Only doses of 20 and 25 mg were effective in lowering pressure, but this drop was accompanied by acute panic reactions, feelings of paranoia, and depersonalization. In an attempt to circumvent the problems of cardiovascular and central nervous system (CNS) side effects, local administration and the use of more soluble and less psychoactive derivatives of THC have been tried.

The majority of studies, especially those done in man, indicate that systemic administration of cannabinoids is needed to produce the degree of decrease in the IOP that is deemed necessary for the treatment of glaucoma. Nevertheless, numerous attempts have been made, using a variety of vehicles, to achieve the desired effect through ophthalmic instillation. Since the isolation and identification of Δ⁹-THC as the major active constituent in marijuana,[23,24] most studies have focused their attention on this compound, which is insoluble in water but soluble in oils; the chemical has also been suspended in a variety of vehicles such as Tween 80 and propylene glycol. Single-drop or multiple topical administrations of 1%Δ⁹-THC in mineral oil produced no significant change in the IOP of subjects free of ophthalmic disease.[25,26] Although Merritt et al. measured a decrease in IOP in glaucoma patients given eye drops of 0.05 or 0.1% Δ⁹-THC, a similar fall in pressure was seen in the contralateral vehicle-treated eye, indicating that systemic absorption was involved.[27]

Several studies have investigated the distribution of Δ⁹-THC in the eye after topical or systemic administration. In rabbits, it was reported that the drug accumulated primarily in the cornea after topical application, and this tissue contained about ten times as much of the label as was found in the iris or the aqueous humor.[28] An in vitro preparation of rabbit tissue demonstrated accumulation of Δ⁹-THC by the anterior uvea.[29] After intravenous administration into rabbits, labeled Δ⁹-THC entered both the vitreous and aqueous humor across the blood-ocular barrier. Intravitreal injections provided evidence for active transport of Δ⁹-THC from the eye. Because of the poor penetration into the human eye of Δ⁹-THC applied topically, water-soluble derivatives were developed. These will be discussed later in this chapter.

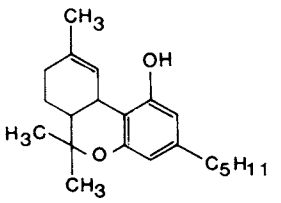
2. Derivatives and Analogs of Δ⁹-THC and Other Cannabinoids

Aside from its lack of activity after topical administration, perhaps the principal drawback associated with Δ⁹-THC as a treatment for glaucoma is its psychoactive properties when it enters the CNS. Using intravenous administration of a number of cannabinoids suspended in human serum albumin, Perez-Reyes and colleagues[30] found

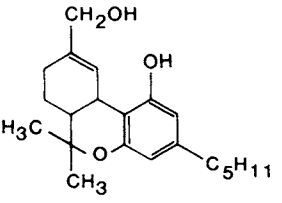
that all of the compounds having a significant effect on IOP also had significant cardiovascular and psychological effects. The order of potency in man for the IOP action was the following: Δ^8-THC > 11-hydroxy-Δ^9-THC > Δ^9-THC > cannabinol > 8-hydroxy-Δ^9-THC. Fewer side effects occurred with Δ^8-THC than with Δ^9 and its metabolite. Only minimal IOP effects were seen with cannabidiol, a cannabinoid lacking psychoactive properties. In rabbits, a similar order was found after intravenous administration: 11-hydroxy-Δ^9-THC > Δ^9-THC > 8-11-dihydroxy-Δ^9-THC > SP111A > 8-11-dihydroxy-Δ^9-THC > 8-hydroxy-Δ^9-THC > several other derivatives tested.[31] (SP111A is a water-soluble form of Δ^9-THC.) A number of other derivatives of THC, as well as cannabidiol, had no effect on the rabbit IOP. In other studies using the intravenous route,[32,33] it was found that Δ^8-THC, Δ^9-THC, cannabinol, and nabilone (a synthetic benzopyran) were active but cannabidiol was not. Although hydroxylated metabolites of Δ^9-THC were less effective than the parent compound, those of Δ^8-THC had more activity. Seven naturally occurring cannabinoids were compared for their ability to lower IOP after topical application to the rabbit eye in sesame oil or light mineral oil.[34] The order of potency in this study was Δ^8-THC > 8-11-dihydroxy-Δ^9-THC > 8-hydroxy-Δ^9-THC > Δ^9-THC > 8-11-dihydroxy-Δ^9-THC > cannabidiol > 11-hydroxy-Δ^8-THC > 8-hydroxy-Δ^9-THC. It is interesting that cannabidiol was found to be effective when given in sufficient concentration (0.1 to 1.0%). Other investigators have reported, however, that Δ^9- and Δ^8-THC, administered topically as a 1% solution in mineral oil, caused erratic responses and had no significant activity.[33]

Green and co-workers[35] studied the structure-activity relationships of a number of cannabinoids and were able to identify several portions of the molecule that are important in the IOP-lowering effect (e.g., C_5H_{11} alkyl side chain). For the interested reader, an excellent study on the stereochemical requirements for cannabinoid activity was reported by Mechoulam and colleagues.[36] A variety of synthetic and semisynthetic compounds have been tested for their ability to lower IOP. Some cannabinoids and their derivatives are illustrated in Figure 2. One derivative (Naboctate; SP-325) lowered IOP in normal volunteers without side effects.[37] An orally effective benzopyran analog of Δ^9-THC, in doses of 2 to 10 mg, was also reported to decrease IOP without significant adverse effects in four subjects.[38] Nabilone, a synthetic benzopyran that resembles the cannabinols, reduced IOP in humans after oral administration but has psychoactive properties.[39] A dihydrostilbene constituent of cannabis (canniprene) has shown promise in preclinical studies.[33]

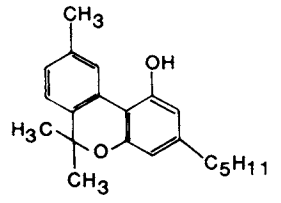
Although many agents seem to possess the ability to lower IOP and thus show potential efficacy in the therapy of glaucoma, relatively little in-depth testing has been done in animals and only a few studies have been carried out in humans. It might be well to consider two points: (1) potency and efficacy are not the same and one must evaluate the utility of a drug in terms of factors such as solubility, safety, duration of action, and maximum effect; and (2) the findings from topical application of drugs to the rabbit eye are not necessarily relevant to the human situation where topical administration of Δ^9-THC is generally not effective. One possible reason for the discrepancy between rabbit and human responses lies in the difference in their blinking rates. Since the degree of absorption of a drug applied to the eye depends on the extent to which it is diluted and washed out by tear fluid, the frequency of blinking can influence the action of the drug.[2] In fact, there are indications that the ocular actions may be species-specific in that intravenous Δ^9-THC had no effect on either IOP or total outflow facility in the rhesus monkey.[35] Furthermore, since glaucoma almost always involves an increased IOP, it would appear preferable to deal with models where the IOP is elevated since numerous drugs from many classes exert measurable actions only under abnormal or pathological conditions. The need for better in vivo and in vitro models is evident.



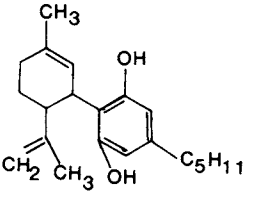
Δ⁹–THC (Δ¹–THC)



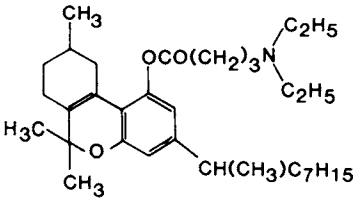
11– OH – Δ⁹– THC



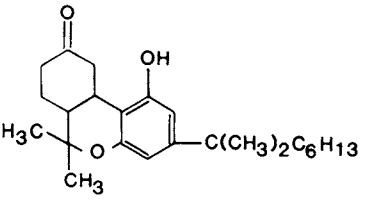
Cannabinol



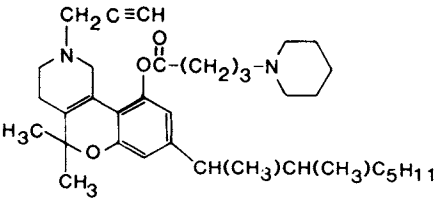
Cannabidiol



Naboctate (SP-325)



Nabilone



Nabitan (SP-106; BW 1464)

FIGURE 2. Some cannabinoids and derivatives.

3. Water-Soluble Compounds

The ability of marijuana to lower the IOP may be due not only to water-insoluble constituents such as Δ⁹-THC, but to water-soluble components as well. A hydrophilic fraction of marijuana, when administered intravenously to rabbits, was able to markedly lower IOP.[40] Topical applications were ineffective. Green and colleagues[41] examined the effects of this water-soluble, noncannabinoid, glycoprotein material and found that it lowered IOP by reducing aqueous humor inflow. Although there was an initial hypertensive phase for the IOP followed by a hypotensive phase, the blood pressure, body temperature, and pO_2 remained constant. There was, however, a decrease in both the blood pCO_2 and pH, indicating that an acidosis might explain some of the fall in IOP. Even at doses which did not produce the blood changes, however,

the IOP dropped as much as 50%. Repeated injections of the material resulted in a diminished effect, thus indicating the possible development of tolerance. Mechoulam et al.[42] synthesized a water-soluble salt of a derivative of Δ^8-THC. When applied topically to eyes of rabbits in which glaucoma had been induced by a drug, this compound lowered IOP about 25 to 30% for 6 hr.[43] It is thought that this THC derivative is rapidly hydrolyzed in the eye to a form which has been shown to have few psychoactive properties in monkeys. Thus, there is the potential for dissociating the antiglaucoma from the CNS effects. In human volunteers, a water-soluble cannabinoid (Nabitan; BW 1464 or 146Y; SP106) given orally produced a drop in IOP that began within 1 hr after administration and reached a maximum at 4 hr. Cardiovascular side effects were observed in a number of subjects, however.[37,44]

4. Tolerance to the Effect of Cannabinoids of IOP

Thus far, we have dealt primarily with the acute effects of cannabinoids on IOP. Since glaucoma is a chronic condition and pharmacotherapy generally involves administration of drugs over a period of years, it is essential that no tolerance develop to the drugs or that any tolerance be small and not progressive. Unfortunately, we have little information in this regard, and what information we do have is somewhat contradictory. For example, studies in rabbits given Δ^9-THC topically to the eye for 60 days revealed no tolerance.[28] The same investigators, however, presented data which indicated that tolerance develops to two analogs of Δ^9-THC (SP-1 and SP-106) tested in the same way (see Figure 1 of Green et al.[45]). Tolerance was also reported to develop to nabilone after 1 week of topical administration to rabbits.[39] With regard to man, it should be realized that many of the acute studies reported in the literature were performed on regular users of marijuana who might be expected to have demonstrated tolerance were it to develop to the action on IOP. In the study by Flom et al.,[17] there was, in fact, an indication of tolerance, since the subjects who used marijuana the most tended to show the least effect. Similarly, it has been reported[46] that human subjects given 10 to 30 mg of Δ^9-THC every 3 to 4 hr for 5 to 21 days showed an initial drop in IOP which lasted for only 10 days before returning to control. IOP was elevated above the pre-drug level 24 to 48 hr after cessation of the drug. On the other hand, Hepler et al. saw no evidence of tolerance or cumulative effects after marijuana smoking in patients observed for up to 94 days.[19] Because the rate and degree of tolerance development to a drug is often dependent on the dose and frequency of administration, however, a lack of correspondence between studies conducted under different conditions should not be too surprising.

5. Mechanism Involved in IOP Effects of Cannabinoids

What about the mode of action of the cannabinoids in lowering IOP? Is there something unique to the cannabinoids that indicates great potential value as drugs to treat glaucoma? As with other drugs, most of what we know in terms of mechanisms comes from studies in animals.

Most animal studies have been conducted in the rabbit, although a number of reports have also appeared using the monkey, dog, and cat. Experiments are conducted in animals with either normal IOP readings or in animals who have had the IOP raised by the administration of any one of a number of agents. Measurements of IOP are usually made with a type of tonometer. For details of the procedures, the reader is referred to the original papers cited in this section.

Earlier in this chapter, we stated that the IOP was a reflection of the balance between the formation and the outflow of the aqueous humor, and we discussed which of these seemed to be the critical factor in the actions of the drugs currently used to treat glaucoma. In trying to reach a conclusion as to the mode of action of cannabinoids in

glaucoma, one is faced with a number of studies that are inconclusive or contradictory. Part of the problem is that our knowledge of the intimate mechanisms involved in aqueous dynamics is still quite rudimentary. Nevertheless, we can examine some of the theories and reach some tentative conclusions.

a. Central vs. Peripheral

Perhaps one should first deal with the question of whether the IOP-lowering effect of the cannabinoids is central or peripheral. Since one of the major influences on IOP is systolic blood pressure, the effect of the cannabinoids on systemic pressure might be thought to be important in their ocular hypotensive action. Yet, no correlation between blood pressure and IOP drop was found.[44] Evidence for a central component to the ocular effect certainly exists. Although studies showing that IOP decreases after topical administration of cannabinoids to rabbits and dogs would seem to indicate that local factors play a significant role, substantial vascular absorption of cannabinoids occurs. For example, in a study in dogs carried out by Merritt and co-workers, eye drops of Δ^9-THC in light mineral oil in a concentration of 0.1 and 1.0% produced a fall in IOP in both the treated and the untreated eye.[47] Similarly, Δ^9-THC, 11-hydroxy-Δ^9-THC, and SP111A reduced IOP in rabbits both in the treated and in the contralateral eye.[31] The time course of effect was the same in both eyes, indicating systemic absorption. Furthermore, significant levels of the drug were present in the plasma after Δ^9-THC was administered to the rabbit eye as a 0.1% solution in a low-viscosity light mineral oil, and the iris of the contralateral eye contained 70% of the amount of THC found in the treated eye.[28] In a study comparing responses in normal and ganglionectomized eyes, Δ^9-THC, SP-1 (a nitrogen-containing analog of Δ^9-THC) and SP-106 (water-soluble form) were applied to rabbit eyes.[45] All lowered IOP bilaterally, despite administration to only one eye. In ganglionectomized eyes, the mean response was 12% as compared to 25% in normal eyes. The investigators attribute this reduced response to the local action of the drug. Whether the response is meaningful, however, is questionable since vehicle effects can be in that range.[32,48] What is clear is that some derivatives of Δ^9-THC have 80 to 100% of their effect in the ganglionectomized eye.[34] On the basis of their work, Green and his colleagues maintain that local actions of some cannabinoids within the eye contribute much to their effect on IOP.

In light of the work by Green, a study by Elsohly et al.[32] is somewhat perplexing. Their work showed that when solutions of 1% Δ^9-THC in various vehicles, including those used by Green, were applied directly to the eye of the rabbit, no drop in IOP occurred. Since all of the studies cited were conducted in rabbits, factors other than species differences must account for the different findings. A report by Chiang and colleagues[48] may provide some explanation. Using both intravenous Δ^9-THC and Δ^9-THC in light mineral oil applied topically to the rabbit eye, they found that drug plasma concentrations increase to maximum values over the first 1 to 2 hr after ophthalmic administration and then decline slowly over the next 24 hr. The variability among animals was great, however. In the papers by Green, the data presented were insufficient to assess the inter- or intraanimal variability. It is possible that this factor could contribute to the discrepancy between the reports.

b. Aqueous Dynamics

What about the effect of the drugs on formation and outflow of the aqueous humor? Delta^9-THC decreased fluid production to about one quarter of normal in in vitro studies on the rabbit eye.[49] In isolated ciliary epithelium, it increased fluid permeability, decreased secretion rate, and decreased net ion transport.[31] Furthermore, in vivo studies indicated that Δ^9-THC increased the total outflow facility of the eye. The overall conclusion was that Δ^9-THC appeared to cause a constriction of the afferent blood

vessels to the ciliary epithelium producing a fall in both blood pressure and flow to the region of aqueous humor formation. These actions result in both a decreased secretion and an increased outflow of aqueous. A study by Merritt et al.,[47] however, found that Δ^9-THC did not facilitate outflow of the aqueous humor, thus suggesting that decreased formation of the aqueous was the principal reason for the drop in IOP. It should be noted that rabbits were used in the former studies and dogs in the latter.

c. Prostaglandins

The idea that some actions of Δ^9-THC are mediated by prostaglandins was first proposed when it was found that a series of naturally occurring cannabinoids were able to inhibit, to varying degrees, the conversion of 8,11,14-eicosatrienoic acid to prostaglandin E_1 (PGE_1) when incubated with bovine seminal vesicle microsomes.[50] The authors speculated that this effect might be responsible for some of the pharmacological actions of the cannabinoids other than their psychoactive properties. A more recent study, however, showed that while low doses of Δ^1-THC (Δ^9-THC) decreased total prostaglandin levels in mouse tumor cells, higher doses elevated them. There is also evidence from several laboratories that cannabinoids may have different effects on PGE than PGF.[51] Based on what we now know as to the effectiveness of a number of cannabinoids in lowering IOP, there seems to be little connection to the synthesis of PGE_1. A direct relationship of inhibition of prostaglandin synthesis to the actions of Δ^9-THC on IOP was suggested by a report that the ocular hypertensive response to arachidonic acid, a precursor of the prostaglandins, is antagonized by Δ^9-THC.[52] However, Δ^9-THC does not interfere with the increase in IOP which follows the administration of prostaglandin E_2. In addition, Δ^9-THC, cannabidiol, and cannabinol caused a dose-related stimulation of arachidonic acid release.[51] Moreover, other drugs which inhibit prostaglandin synthesis, such as aspirin and indomethacin, do not reduce IOP.[53] Although the relationship between prostaglandins and IOP is not fully understood, it does not appear likely that Δ^9-THC exerts its ocular actions through prostaglandin inhibition.

d. Transmitter Systems

As discussed earlier in this chapter, the actions of certain drugs on alpha and beta adrenergic receptors are thought to be the principal mechanisms involved in their ability to lower IOP. Similarly, it is thought that such actions may also be involved in cannabinoid effects. Green and Kim[54,55] found that pretreatment with phenoxybenzamine, an alpha-adrenergic blocker, blocked the effects of Δ^9-THC on total outflow facility. On the other hand, propranolol, a nonselective beta antagonist, was ineffective. Nevertheless, both blockers were able to reduce the drop in IOP caused by Δ^9-THC. Green's group,[45,54,56] interpreted the results to mean that cannabinoid-induced effects had two components, an alpha-adrenergic-mediated increase in total outflow facility and beta-mediated decrease in formation of the aqueous humor. The difficulties in accepting such a hypothesis are discussed by Korczyn,[57] who points to the problems of variability in animal response, lack of determination as to whether the effects of Δ^9-THC on the IOP are central or peripheral, the lack of development of a supersensitivity to the actions of Δ^9-THC after either preganglionic or postganglionic denervation, and the difficulties of drawing firm conclusions based almost solely on the use of blocking drugs.

In addition to the proposed effects on the adrenergic nervous system discussed above, there have also been several suggestions that part of the actions of cannabinoids may be explainable in terms of other transmitter systems. For example, it has been reported that Δ^9-THC and other cannabinoids can alter the binding characteristics of several different receptors such as D_2 and D_3 dopamine receptors,[58] and that both

chronic Δ^8-THC and Δ^9-THC treatment modify the serotonergic system.[59] Whether changes in these or other transmitter systems are part of the mechanism by which the cannabinoids alter IOP is not known, primarily because we know so little about the possible role that these systems play in regulating the IOP either directly or indirectly.

IV. OTHER EFFECTS OF CANNABINOIDS ON THE EYE

The focus in this chapter has been on the effects of cannabinoids on intraocular pressure. Indeed, even the brief discussion of the anatomy and physiology of the eye was geared towards understanding how cannabinoids can lower IOP. One reason for this emphasis is that the only therapeutic role thus far proposed for cannabinoids relative to ocular effects is in the treatment of glaucoma. The other reason is that we know very little about other ocular effects of this class of compounds. It seems appropriate, however, to consider what has been reported in this area.

One action for which some information is available relates to change in pupil size. (The reader should recall references made earlier in this chapter to the relationship between the treatment of glaucoma, particularly the angle-closure type, and change in pupil size induced by pharmacological agents.) The literature on the effects of cannabinoids on pupil size is, however, far from clear. For example, clinical studies have found effects ranging from miosis to mydriasis. Brown et al.[60] reported a 7.4% reduction in pupil diameter 40 min after subjects had smoked 15 mg of Δ^9-THC, and Hepler et al.[61] found a significant decrease in mean pupillary diameter measured 5 min after experienced users had smoked 2 g of marijuana over a 30-min period. However, Hepler et al. found no significant miosis in a subsequent study.[19] Another group saw no change in pupillary size of healthy subjects who ingested Δ^9-THC by smoking (50 to 200 μg/kg) or orally (120 or 480 μg/kg);[62] nor was any change in pupil size seen with 0.5 or 2 g of smoked marijuana in healthy, drug-naive males.[63] Yet, a slight but significant increase in pupil size lasting up to 70 min has been noted in long-term users who smoked large doses of THC.[64] Among the reasons for the discrepancies in these studies may be differences in subject population (i.e., healthy volunteer vs. hospital patient or drug user vs. nonuser) and testing procedures. Ambient light levels are important in this regard, as are the number and frequency of measurements made of the pupil size before and after drug administration. If the pupil response to cannabinoids is not a sustained one but fluctuates about a higher or lower level, as is the case for opioids in a number of species,[65] then the methodological differences assume additional importance. In the rat, for example, a dose-related mydriasis with Δ^9-THC occurs, although the minimum dose for this effect was 5 mg/kg in one study[66] while doses greater than 50 mg/kg were required in another study.[67] To a large extent, these potency differences are probably attributable to the use of different vehicles (Tween 80 vs. Emulphor EL620, respectively). Yet, when examined with an infrared video-pupillometer system on line with a computer, measurement of pupil size every 5 sec revealed that fluctuations in pupil size can occur with the cannabinoids. Thus, apparently conflicting studies in man based on just a few photographs or measurements taken prior to and following drug ingestion may be looking at different parts of the same response.

Effects of cannabinoids on other parameters of ocular function have been examined to an even lesser extent than IOP or pupil size. Some of these are listed in Table 1. Photophobia, hyperemia of the conjunctival blood vessels, and decreased lacrimation are common findings among marijuana smokers. The inhibition of tear flow can precipitate a host of other ophthalmologic problems including corneal ulceration, conjunctivitis, and keratitis. It may also underlie the frequent complaints of discomfort among contact lens wearers who smoke marijuana. In two studies, Hepler and his colleagues saw no change in the pupil response to strong light, in Snellen visual acuity,

Table 1
REPORTED OCULAR EFFECTS OF CANNABINOIDS IN MAN

Decreased intraocular pressure
Photophobia
Hyperemia of conjunctiva
Decreased lacrimation
Corneal ulceration
Conjunctivitis
Keratitis
Small change in pupil size

or in refractive error, color vision, degree of phoria, stereoscopic perception or fusion, visual fields, ophthalmodynamometry, or the electroretinogram.[19,61] Shapiro noted a circumcorneal ciliary injection, prominence of corneal nerves, photophobia with blepharospasm, and ocular irritation (burning, dryness, and redness) in habitual users.[16] In contrast to Hepler et al., Shapiro noted a decrease in distant visual acuity as well as in accommodation for near vision. Another study showed that a subject's ability to detect brief light flashes was impaired by 2 to 3 mg of smoked marijuana, although other visual functions which depended on eye movements were not affected.[3] A study on a large number of marijuana users and nonusers in Costa Rica found that small, but statistically significant, increases in basal lacrimation, IOP, and photosensitivity were present in users along with decreases in color-match limits and Snellen acuity.[68] On the other hand, there were no significant differences between users and nonusers in incidence of pathological fundus signs, conjunctival hyperemia, or color-match midpoints.

With regard to animal studies, cannabinoids caused decreased lacrimation, corneal opacity, keratitis, conjunctivitis, corneal ulceration, and prolapse of the iris in dogs.[69] Colasanti and colleagues investigated the actions of Δ^9-THC and cannabichromene on IOP and ocular toxicity after administration unilaterally to the cornea of cats either acutely by eye drops or chronically by minipumps over a period of 9 days.[70] With Δ^9-THC dissolved in PEG 400, the IOP continued to decrease in both the treated and untreated eye during the 9 days of chronic treatment (20 μg/hr), but conjunctival chemosis, erythema, and hyperemia accompanied the treatment while corneal opacities became evident within 3 or 5 days. Neither the vehicle nor cannabichromene affected IOP or produced the toxic effects.

Those few studies that have been reported on the ocular effects of cannabinoids have failed to indicate any potential therapeutic effect on the eye other than lowering IOP. Furthermore, there is reason to recommend that if chronic use of cannabinoids in the treatment of glaucoma is contemplated, careful monitoring of the patient should be an essential part of the regimen in order to minimize chances of ocular side effects as well as to obviate any possibility of general systemic effects such as tachycardia, postural hypotension, and undue central nervous system actions.

V. SUMMARY AND CONCLUSIONS

There is no doubt that marijuana and several cannabinoids, particularly Δ^9-THC, are able to lower the intraocular pressure, and this action certainly justifies their study as potential therapeutic agents for the treatment of glaucoma. However, some of the problems associated with their use make it apparent that synthetic or semisynthetic analogs of the cannabinoids will be needed before there is general acceptance of their role in medical therapy. Perhaps the two principal deficiencies associated with Δ^9-THC

as a treatment for glaucoma are its psychoactive properties when it enters the central nervous system and its inability to penetrate the human eye when administered topically. This latter property is related to the fact that it is totally insoluble in water, thus presenting problems with proper formulation. In this regard, further experimentation with water-soluble derivatives and with other vehicles for topical application of cannabinoids is needed since this is the route of administration that is undoubtedly desirable for the long-term therapy of glaucoma. At the moment, however, the drugs seem to produce an adequate IOP-lowering effect only when given systemically, routes of administration that are generally unacceptable because of the broad range of actions produced by the cannabinoids and their derivatives. Throughout this chapter, attention was focused on the effects of Δ^9-THC and its possible mechanisms of action. Although this agent is the principal cannabinoid in marijuana and undoubtedly accounts for most of its effects, numerous other pharmacologically active chemicals are present in the plant. Information about chemicals other than Δ^9-THC is quite incomplete. Even more deficient is our knowledge of the long-term effectiveness of cannabinoid treatment on glaucoma. Merely lowering the IOP, even without producing cardiovascular and CNS side effects may not be sufficient to prevent loss of vision. Despite the efficacy of drugs such as pilocarpine and timolol, we are far from having an ideal agent for the pharmacotherapy of glaucoma. Whether or not the cannabinoids will provide a useful alternative or supplement to our present pharmacological armamentarium remains to be seen.

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