Mydriasis induced by tetrahydrocannabinol (THC) in rats. AMOS D. KORCZYN AND YECHIEL ESHEL.

Male albino rats, injected intravenously or intracerebroventricularly with Δ_1-THC, develop mydriasis. The median effective dose of the intravenous administration group was 5 mg/kg THC, whereas that for the intracerebroventricular route was 150 μg/kg THC. Sympathectomy significantly decreased the THC-induced mydriasis. The mydriatic effect was not influenced by naloxone. We conclude that THC produces mydriasis through a central action, the efferent pathway of which is the sympathetic system. (INVEST OPHTHALMOL VIS SCI 22:408-410, 1982.)

Among the several known biological actions of cannabinoids, the observation of a decrease of intraocular pressure (IOP) has created interest for its potential therapeutic use in glaucoma. The mechanism underlying the fall of IOP has been studied, but the complete picture is still unclear. A prevailing view is that cannabinoids interact with the sympathetic system. We have attempted to study the effects of tetrahydrocannabinol (THC) on the ocular sympathetic system by investigating the pupillary action in rodents. In humans, the pupillary action of THC is controversial. For several years it was believed that marijuana smoking causes miosis. Hepler et al., who were apparently the first to study the pupillary effects under controlled conditions, observed miosis. However, another article maintains that mydriasis occurs, and a more recent study by Hepler et al. claims that although miosis occurs, it is slight and does not reach statistical significance. The controversy may be due to differences in the conditions under which the experiments were performed as well as to differences in drug purity. We have examined the effect of the active ingredient of cannabis, Δ_1-THC (also known as Δ_9-THC).

Methods. Male Charles River albino rats weighing 300 to 400 g were used. Pupillary size was measured as previously described. Briefly, nonanesthetized animals were observed under a Zeiss operating microscope, the ocular of which was equipped with a ruler and a 30 W bulb placed 15 cm from the rat's eye and equipped with 2.6 diopter lens, giving an illumination of 33 cd/m². Δ_1-THC (Makor Chemicals, Jerusalem, Israel) was dissolved in 5% Tween 80 solution in 0.9% NaCl and injected intravenously (0.2 ml) through a tail vein. Each milliliter of the injected solution contained 3 to 40 mg THC according to the weight of the rat and the dose administered. Intracerebroventricular (ICV) injections were performed on anesthetized rats (chloral hydrate 400 mg/kg) after trephination 2 mm lateral to the bregma. The volume of ICV injections was 50 μl. Each milliliter of the solution injected contained 0.6 to 2.4 mg THC. Control animals were injected similarly with solutions lacking THC.

Ocular sympathectomy was produced unilaterally by removal of the superior cervical ganglion at least 1 week prior to THC administration. Naloxone (10 mg/kg) was injected intraperitoneally 10 min prior to determination of pupillary size.

Results. Intravenous injections of THC caused a dose-dependent mydriasis that reached a maximum of three times the baseline at a dose of 10 mg/kg (Fig. 1). The effect of 10 mg/kg THC administered intravenously reached a maximum within 1 min and lasted for about 30 min. Sympathectomy significantly inhibited the response to THC; after 10 mg/kg THC administered intravenously the denervated pupil dilated by only 60% (Fig. 1).

ICV administration of THC also caused mydriasis (Fig. 2). The median effective dose at this route of administration was 150 μg/kg compared to 5 mg/kg after intravenous administration. This central effect was similarly inhibited by previous sympathectomy.

Application of THC solution (340 mg/ml) to the eye of the rat (in a volume of 0.05 ml) did not affect pupillary size. Naloxone (10 mg/kg i.p.) failed to prevent or abolish THC-induced mydriasis.

Discussion. Our data demonstrate that in rats...
THC produces dose-dependent mydriasis. The pupillary dilatation has a short latency and its duration is about 30 min. This effect is probably of central origin, since ICV injections produced similar results with administration of less than 1% of the systemic dose (Fig. 1). It is interesting that after intraperitoneal injections of THC, 1% of the drug injected reaches the brain. The effects of ICV injections were somewhat more prolonged than those of systemic administration. On the other hand, local application of THC to the eye failed to affect pupillary size.

The mydriatic response was practically inhibited by cervical sympathectomy, indicating that the sympathetic system is a major efferent pathway of this effect. This is in contrast to the mydriasis caused by opiates, which is not affected by sympathectomy. This latter response is thought to occur by abolition of parasympathetic tone. THC mydriasis is not reversed by naloxone, thus differing from the pupillary dilatation induced by opiates and enkephalins.

The reason that THC mydriasis is not abolished completely by cervical sympathectomy is unclear. It could be due to the fact that the sympathectomy is incomplete and some aberrant fibers remained intact. Alternatively, this portion of the mydriasis could involve other mechanisms such as inhibition of parasympathetic outflow to the eye. The increase of the sympathetic tone that mediated THC-induced mydriasis in our experiments is paralleled by a similar phenomenon in the cardiovascular system of rats and of humans.

It must be stressed that the effects we observed in rats may not be directly applicable to other species, particularly humans. This is mainly because we used doses that are much higher than those taken by humans. On the other hand, a greater sensitivity in humans is typical of most drugs acting on the brain. It is also possible that under the conditions of our study, a slight miosis, resulting from low concentrations, would not be observed because of the light reflex.

The ocular hypotensive action of THC was shown to be inhibited by sympathectomy. It is therefore possible that both the effects on pupillary size and on IOP are underlain by similar mechanisms, and it is interesting to speculate about a similarity with clonidine, the central actions of which are mydriasis and decrease in IOP.

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Comparative ocular pathogenicity of Cryptococcus neoformans, Candida glabrata, and Aspergillus fumigatus in the rabbit.

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In a previous study, 88% of rabbits with disseminated infection caused by Candida albicans developed ophthalmoscopically visible, hematogenous endophthalmitis (chorioretinitis) over a 2 week period. To determine the incidence of this ocular complication in disseminated infection caused by Cryptococcus neoformans, Candida glabrata, and Aspergillus fumigatus compared with that caused by C. albicans, the first three species of fungi were injected intravenously (between 10^6 and 10^9 organisms per animal) into 36 New Zealand white rabbits. No choriotecinal lesions were seen by indirect ophthalmoscopy over a 2 week period. C. glabrata and A. fumigatus were not cultured from chorioretinas despite positive cultures from brains and kidneys at 1 and 2 weeks. In contrast, C. neoformans was cultured from 12 of 18 chorioretinas (mean Log_10 3.45 colony forming units/gm of tissue) as well as from the brains and kidneys. The less intense inflammatory cell response to C. neoformans compared with that to C. albicans seen on histopathologic examination most likely explains the nondetectability of the cryptococcal chorioretinitis by indirect ophthalmoscopy. These data suggest that C. glabrata, A. fumigatus, and possibly C. neoformans have less ocular pathogenicity than C. albicans in rabbits and correlate with the small number of documented human ocular responses to brain stimulation in freely moving rats. Eur J Pharmacol 65:65, 1980.

References