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An update on cannabis research

S. HUSAIN
Department of Pharmacology, School of Medicine, University of North Dakota, Grand Forks, North Dakota, United States of America

I. KHAN
Division of Mental Health, World Health Organization, Geneva, Switzerland

ABSTRACT

A symposium of over 125 scientists, held in August 1984 at the campus of Oxford University, considered the latest developments concerning cannabis research. Evidence on the mode of tetrahydrocannabinol action on the central nervous system indicates that acetylcholine turnover in the hippocampus through a GABA-ergic mechanism is of major importance, though the role of the dopaminergic or serotoninergic mechanism and involvement of prostaglandins and c-AMP is not ruled out. The use of cannabis causes prominent and predictable effects on the heart, including increased work-load, increased plasma volume and postural hypotension, which could impose threats to the cannabis users with hypertension, cerebrovascular disease or coronary arteriosclerosis. Cannabis or tetrahydrocannabinol has damaging effects on the endocrine functions in both male and female of all animal species tested. Among possible mechanisms of action, it is suggested that tetrahydrocannabinol disrupts gonadal functions by depriving the testicular cells of their energy reserves by inhibition of cellular energetics, and that it stimulates androgen-binding protein secretion, which may account for oligospermia seen in chronic cannabis smokers. In addition to these direct effects on gonads, tetrahydrocannabinol interferes with hormonal secretions from the pituitary, including luteinizing hormones, follicle-stimulating hormones and prolactin. Research findings indicate that maternal and paternal exposure to cannabinoids can influence developmental and reproductive functions in the offspring, but it is difficult to separate possible teratogenic effects from subsequent gametotoxic and mutagenic potentials of cannabinoids.

The use of tetrahydrocannabinol for the treatment of emesis and glaucoma are the only therapeutic applications of cannabinoids proven to date, though research on the possible use of cannabinoids for the treatment of convulsion, pain and anxiety is being carried out.

Introduction

Over 125 scientists from various parts of the world met from 6 to 8 August 1984 at a symposium, which was held at the campus of Oxford University, United Kingdom of Great Britain and Northern Ireland, to present the results of their research on cannabis and to discuss the latest advances and future directions of such research. This was a satellite symposium of the Ninth International Congress of Pharmacology. The symposium was sponsored by the World Health Organization, Geneva, Switzerland, and supported by the Lilly Research Center, United States of America, and Astra Lakemedel AB, Sweden.

This article summarizes information presented at the symposium, which focused on the following: pharmacokinetics and metabolism of cannabinoids; analysis and detection of cannabinoids in biological fluids; the effects of cannabinoids on neurochemical, physiological, cellular, endocrine and developmental processes; and clinical and therapeutic applications of cannabinoids.

Pharmacokinetics and metabolism of cannabinoids

Among other key topics relating to current research on cannabis, the scientists at the symposium considered the pharmacokinetics and metabolism of Δ^9-tetrahydrocannabinol (THC) and other cannabinoids. S. Agurell of Astra Lakemedel AB and Karolinska Institute, Sweden, indicated that in man, THC produced a similar plasma profile after smoking or intravenous administration. A cigarette containing 10 – 20 mg of THC after smoking immediately produced a plasma THC level of approximately 100 ng/ml which then decreased rapidly and during the terminal elimination its disappearance slowed down. Although it took 30 days for a single dose of THC to be eliminated from the body with a tissue half-life of seven days, Agurell and others had estimated that the terminal half-life in plasma was between 20 and 36 hours. In heavy cannabis smokers, the systemic availability of THC was 23 per cent $\pm$16 per cent as compared with 10 per cent $\pm$7 per cent in light users. The average plasma clearance value for heavy and light users was high (950 ml/min). THC is initially metabolized in man in a similar way as in most animals with a preferential allylic oxidation to 11-OH-THC. Side chain hydroxylation and epoxide formation appear to be marginal in humans ([1], pp. 165 – 183). I. Yamamoto of Hokuriko University, Japan, suggested that THC was biotransformed in substantial amounts to its epoxide by the monoxygenase system of the guinea pig liver ([2], p. 22). M. Wall of the Research Triangle Institute, United States, discussed the metabolism of orally administered tritium Δ^8- and Δ^9-THC in humans. In the Δ^8-series, the hydrolysed form in plasma which corresponded to the conjugate glucuronide ester, constituted only 10 – 20 per cent of the

unconjugated 11-nor-Δ^8-THC-9-carboxylic acid. On the other hand, in the Δ^9-series, unconjugated and conjugated 11-nor-Δ^9-THC carboxyglucuronide were found in approximately equal proportions. In all cases, the ether soluble extract of urine contained only the conjugate 11-nor-Δ^8 (Δ^9)-THC-9-carboxyglucuronide both in the Δ^8- and Δ^9-series ([2], p. 5).

The pharmacokinetics of cannabidiol (CBD) was reported to be similar to THC in man, while its systemic availability, plasma clearance and volume of distribution were found to be higher than for THC. On the other hand, the systemic availability of cannabinol (CBN) in plasma was almost twice that of THC, four hours after smoking ([2], p. 4).

Analysis and detection of cannabinoids in biological fluids

Measurements and detection of cannabinoids and their metabolites in biological fluids is important both for establishing the pharmacokinetic parameters and for forensic purposes. Because of the rapidity with which THC is metabolized in the body, it is more appropriate to determine the presence of a metabolite rather then the presence of the parent drug in fluids such as urine. Recently, this has been done to obtain evidence of cannabis use. The screening techniques, radioimmunoassay and enzyme immunoassay are used to analyse urine for the presence of 11-nor-THC-9-carboxylic acid (THC-COOH), the major urinary metabolite of THC. Positive results of these methods, are confirmed by other techniques, some of which are indicated below. D. Harvey of Oxford University who was the main organizer of the symposium, described the developments in mass spectrometric detection technique including the use of high resolution or metastable ion monitoring to achieve greater selectivity and sensitivity. He also described the use of negative-ion chemical ionization mass spectrometry with suitably derivatized cannabinoid molecules. This technique is capable of detecting THC at the 0.02 pg range and has been used to measure the drug in plasma to 100 pg/ml ([1], pp. 291 – 308). Different methods of verification of cannabis have their limitations. The advantages and limitations of four confirmatory procedures, namely high-performance liquid chromatography, gas chromatography/flame ionization detector (GC/FID), gas chromatography/electron capture detector (GC/ECD) and gas chromatography/mass spectrometry, were discussed by M. ElSohly of University of Mississippi. The GC/FID procedure currently available for the analysis of acid metabolite, THC-COOH, in human urine has a poor sensitivity and necessitates the use of large volumes of urine, an elaborate clean-up procedure, tremendous sample concentration ($\times 500$), and injection of a large portion of the sample into the gas chromatograph. On the other hand, GC/ECD is found to have higher sensitivity and reproducibility requiring shorter time for analysis, minimum sample preparation and only a small volume of urine ([3], pp. 262 – 264; [4], pp. 7 – 9).

In the analysis of cannabinoids from biological fluids, isolation and derivatization are the two most common and necessary steps. In these analyses, the isolation step is relatively easy to automate. In contrast, the analytical derivatization step is laborious and frequently requires considerable technical skill. A method for impregnating Amberdite ion exchange resin, XAD-2 with pentafluorobenzyl bromide was described by J. Rosenfeld of McMaster University, Canada. This method permits the simultaneous extraction and derivatization of cannabinoids from samples ranging from aqueous fluids to the solid and insoluble resin. The pentafluorobenzyl (PFB) derivatives are recovered by isolating the resin (filtration) and elution of reaction products with organic solvent. This procedure has a high optimum yield of 85 per cent for both monofunctional (THC, 11-OH-THC) and bifunctional (CBD) cannabinoids. It also offers a potentially important alternative to phase transfer catalysts for simultaneous extraction and conversion of cannabinoids to PFB derivatives preparatory to GC with ECD or detection by negative-ion chemical ionization mass spectrometry ([1], pp. 151—161).

Effects of cannabinoids on neurochemical, physiological and cellular functions

To unravel the mechanism of THC action at the level of the central nervous system, its effects on different neurotransmitters have been studied extensively. However, the mode of action of THC is still a puzzle. Recent evidence seems to indicate that acetylcholine turnover in the hippocampus through a GABA-ergic mechanism is of major importance, but the role of a dopaminergic mechanism and involvement of prostaglandins and cyclic adenosine-3,5-monophosphate (cyclic-AMP) is not yet ruled out. Similarly chronic THC treatment of rats appears to alter the brain levels of 5-hydroxytryptamine (5-HT) and these animals show spontaneous 5-HT behaviour. Because Δ^8- and Δ^9-THC are structurally similar, D. A. Taylor of Victorian College, Australia, had investigated the comparative effects of chronic treatment with these two cannabinoids on clomipramine and 5-HT behaviour in rats. Clomipramine was able to induce less behavioural changes in Δ^8-THC treated rats than in Δ^9-THC treated rats. On the other hand, 5-HT induced wet-dog shakes were greater in Δ^8-THC treated rats than in Δ^9-THC treated rats. Although ketanserin inhibited the 5-HT behaviour, there was no change in the number of 5-HT_2 receptor binding sites. There was, however, a reduction in the number of dopamine binding sites in the corpus striatum of Δ^8-THC treated rats. Taylor suggested that both chronic Δ^8-THC and Δ^9-THC treatment appeared to modify the serotoninergic system, but the extent of these modifications were not constant. These behavioural changes probably result from a combination of different actions on different transmitter systems by Δ^8-THC or Δ^9-THC ([5], pp. 240—245).

The clinical importance of these experiments is still uncertain and the long-term effects of chronic cannabis use on the human central nervous system remain controversial. Montgomery and Moss of the University of Texas (El Paso) have studied the effects of THC and levonantradol (LEVO), a synthetic analogue of THC, on reserpine (RES)-induced hypokinesia in rats. RES-induced hypokinesia is a well-studied animal model for Parkinson's disease. Both THC and LEVO were able to potentiate significantly the RES-induced hypokinesia. This THC/RES hypokinesia was not blocked by L-DOPA, but was dramatically reduced by ethopropazine, an anticholinergic drug. Surprisingly, other cholinergic drugs except nicotine do not alter this hypokinesia. It appears that the action of THC in the extrapyramidal system is a minor subtle effect that is masked by the function of the main dopamine (DA) system. When the DA system is blocked, for example by RES or haloperidol, the normal occult effects of THC, LEVO and nicotine become observable. It is, therefore, suggested that THC affects extrapyramidal function, either directly or indirectly, through a cholinergic mechanism that is possibly nicotinic ([2], p. 9).

Due to the high stereospecificity of THC and its interactions with several neurotransmitters, investigators have commenced looking for cannabis receptors to explain its effects.

C. Hillard of the Medical College of Wisconsin has carried out receptor-binding studies of β-adrenergic, dopamine and opioid receptors, which indicated that THC and other cannabinoids were able to alter the binding characteristics of certain receptors with which THC seemed to interact uniquely. According to Hillard, these receptor changes may be due in part to cannabinoid-induced changes in membrane environment in which neurotransmitter receptors reside. Membranes may serve as a transducer of cannabinoid action ([1], pp. 591–602). Similarly, Nye and others of Johns Hopkins University, have studied the *in vitro* binding of ^{3}H-5′-trimethyl ammonium Δ^{8}-THC (^{3}H-TMA) to rat neuronal membranes. ^{3}H-TMA bound saturably to brain membranes, but the process was reversible, and numerous detergents would solubilize the sites without altering their pharmacological properties. The binding was potently inhibited by Δ^{9}-THC. Such inhibitory potency of THC for ^{3}H-TMA sites parallels its potency in behavioural and physiological tests. Several behaviourally inactive cannabinoids such as cannabinol and cannabidiol also show activity at ^{3}H-TMA binding sites and, based on these findings, Nye and others postulate that these drugs may behave as antagonists to THC as suggested by other physiological and behavioural studies ([2], p. 34).

Effects of cannabinoids on the cardiovascular system

Cannabis causes prominent and predictable effects on the heart. R. Jones of the University of California has found that acute THC causes

increased heart rate, orthostatic hypotension and supine hypertension in humans. Most other mammals, on the other hand, show bradycardia and decreased systemic arterial pressure after the administration of THC. These effects probably have their origin in the central nervous system, though peripheral neurostructures and adrenal medulla may also be altered. These cannabis-induced changes in the heart, including increased work-load, increased plasma volume and postural hypotension could impose threats to cannabis users with hypertension, cerebrovascular diseases or coronary arteriosclerosis. Jones suggested that cannabis users should carefully consider adverse interactions of cannabis with different cardioactive drugs such as atropine, β-blockers, and diuretics ([2], p. 38). R. Trouve of the Fernand Widel Hospital, France, and G. Nahas of Columbia University, United States, also presented evidence of the adverse affects of cannabinoids on cardiac functions. They indicated that THC had a biphasic effect on cardiac frequency in isolated Langendorff rat heart preparation. At low THC doses, cardiac frequency was decreased while at higher THC concentration it was increased; THC also caused a decrease in contractile force and progressively reduced the coronary blood flow. In these studies, CBD produced a dose-related increase in cardiac frequency and a marked increase in contractile force and coronary blood flow. These antagonistic effects of THC and CBD might explain the variability in cardiovascular response to cannabis, which contains a diverse mixture of these two cannabinoids. On the other hand, it is speculated that CBD might also have some useful cardiovascular properties ([6], pp. 191–194).

Effects of cannabinoids on the immune system

At present, there is suggestive evidence that the use of cannabis or THC can lead to dysfunction of the immune system in humans. In animals, there is conclusive evidence that THC causes immunological defects when inhaled or given parenterally. In rodents, this effect has been correlated with decrease in host resistance to selected bacteria and viruses. Cabrel, Holsapple and others have studied the effects of THC on host resistance to herpes simplex virus type 2 (HSV-2) vaginal infection in guinea pigs and mice. In comparison with controls, THC (4 and 10 mg/kg, intraperitoneally) significantly increased lesions and mortality in guinea pigs inoculated with HSV-2. Utilizing a five-day THC exposure regimen in mice, these investigators pre-immunized guinea pigs with herpes simplex virus type 1 (HSV-1). The rationale for pre-immunization was based on the recognition that prior infection with HSV-1 should provide partial immunity to subsequent exposure to HSV-2, a situation which mimicked human infection. Mice received an intravaginal challenge of an HSV-2 (LD_{80}) on the second day of THC exposure. On the eighth day of post HSV-2 challenge, lethality was 25 per cent in treated as well as in untreated virus control mice. In treated mice with THC doses of 5, 25 and 100 mg per kilogram intraperitoneally the

lethality increased to 32.5, 50 and 100 per cent respectively. These results suggested that the decrease in resistance to HSV-2 infection following exposure to THC might be associated with a decreased humoral immunocompetence. In this connection, the role of adrenal steroids in the immunosuppressive action of cannabinoids is not clear. It is believed that a cannabinoid-induced increase in corticosteroid release may mediate certain aspects of immune suppression, such as splenic atrophy, but not the inhibition of antibody formation ([2], p. 36; p. 40).

Effects of cannabinoids on endocrine and reproductive functions

Evidence that has accumulated during the last ten years indicates that the use of cannabis or THC has damaging effects on the endocrine functions of both male and female in every species. Evidence also shows that the administration of cannabis or THC to laboratory animals influences their developmental processes. In reviewing the effects of cannabinoids on the neuroendocrine and reproductive functions, H. Rosenkrantz of Mason Research Institute, United States, indicated that despite disagreements between and within human and animal studies, there was definitive evidence to prove the aberrations of sexual behaviour, hormone imbalances, cycle derangements, inhibition of ovulation, interference with spermatogenesis including embryotoxicity, weak teratogen signs, delayed post-natal development and chromosomal anomalies ([2], p. 51).

In the male, various synthetic cellular processes including spermatogenesis and sperm motility have been shown to be inhibited by THC. Since all these cellular processes require energy for their successful completion, S. Husain of the University of North Dakota suggested that THC has an inhibitory effect on the utilization of energy-rich substrates in the testis. His *in vitro* and *in vivo* studies of rats treated with THC doses of 5, 10 and 20 mg per kilogram per os for 15 days showed that glucose and fructose oxidation and uptake of glucose into the testicular cells were greatly inhibited. On the basis of these observations it was suggested that THC disrupted many gonadal functions by depriving the testicular cells of their energy reserves through inhibition of cellular energetics ([7], pp. 391–398). S. Holmes and R. Smith of Baylor University, United States, proposed another mechanism by which cannabinoids might interfere with spermatogenesis. They studied the basal levels of androgen-binding protein (ABP) secretion in rat Sertoli cells after exposure to THC in the medium. THC stimulated ABP secretion in a dose-dependent manner. Since ABP has a high affinity for androgens, the increased concentration of ABP produced by THC resulted in an increased binding of testicular androgens and decreased concentration of free androgens; androgen target cells became hypoandrogenic. It is proposed that this hypoandrogenicity may be responsible for the oligospermia seen in chronic cannabis users ([2], p. 55).

In addition to these direct effects on gonads, THC is shown to interfere with hormone secretion from the pituitary. It blocks the surge in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretions necessary for ovulation and maintenance of the follicular phase. Similarly, L. Tyrey of Duke University, United States, showed that in rats basal prolactin (PRL) secretion being under control by the hypothalamus was reduced by THC treatment. As in the case of LH, THC suppressive effects on PRL are not attributable to the inhibition of the hormone secretion at the pituitary level. This is because THC is ineffective in reducing PRL secretion from pituitary tissue incubated *in vitro* or transplanted to an ectopic site *in vivo* ([2], p. 52).

J. Harclerode of Bucknell University, United States, describing the effects of THC on rat serum and pituitary growth hormone, indicated that there was an initial depression of pituitary growth hormone after acute THC exposure and that long-term exposure resulted in decreased release of growth hormone from the pituitary. The consequences of long-term THC exposure were reversible because growth hormone levels in the pituitary return to normal following cessation of drug exposure ([2], p. 20). E. Field and L. Tyrey of Duke University have studied the effects of chronic treatment of female rats with THC on their pubertal development and found that THC delayed the onset of vaginal cornification and the occurrence of the first ovulation by 4.3 ± 0.9 days. In view of the known inhibitory effects of THC on pituitary function and the recognized importance of pituitary gonadotropins in the development of ovarian cyclicity, it seems likely that this sexual maturational delay results from altered neuroendocrine function in the pubertal animal ([2], p. 53).

In view of the wide range of effects of cannabinoids on reproductive functions, it has been logical to ask if these compounds are gametotoxic. S. Dalterio of the University of Texas Health Science Center has studied the effects of exposure to cannabinoids during the pre-gestational period of adult male mice on their subsequent fertility, endocrine profiles and the cytogenic characteristics of their germ cells, as well as on their male offspring. Repeated exposure of male mice to THC, CBD or CBN resulted in decreased fertility as indicated by pre-natal and neonatal deaths or failure to impregnate known fertile females. When male offspring of these cannabinoid-treated fathers were examined, 36 per cent of them from THC-exposed fathers and 21 per cent from CBN-exposed fathers failed to achieve a normal conception. Moreover, these offspring exhibited cytogenic abnormalities quite similar to those observed in their sires. In litters sired by two male offspring from THC-exposed fathers, severe congenital defects were observed, one with exencephalic fetus and the other a pup with exencephaly, spina bifida and intestinal eventration. These results suggest that paternal exposure to cannabinoids can alter the reproductive parameters in the offspring. Similarly, it has been shown that maternal exposure to cannabinoids produces long alterations in pituitary gonadal functions in male and female offspring. It is however, difficult to separate possible

teratogenic effects from subsequent gametotoxic and possibly mutagenic potentials of cannabinoids ([1], pp. 411–425).

Clinical and therapeutic applications of cannabinoids

During the 1970s, a great deal of basic and clinical research was conducted to see if THC and similar synthetic cannabinoids have any therapeutic applications. L. Lemberger of Lilly Research Laboratories, United States, and J. Trounce of Guy's Hospital, United Kingdom, presented a comprehensive review of progress made in this area. In the past, THC has been purported to be a potentially useful new drug for the treatment of hypertension, asthma, cancer, infection, endogenous depression, epilepsy, pain, anxiety, glaucoma and emesis. With the advancement in the knowledge of cannabis, most of these claims have not been proven, except for the use of THC as an anti-emetic and for the treatment of glaucoma. Research on a possible use of cannabinoids for the treatment of convulsions, pain and anxiety is underway ([2], p. 76; p. 79).

THC and Nabilone have been in clinical use as anti-emetics in patients receiving different chemotherapeutic regimens. Studying the efficacy of THC, R. Gralla of Cornell University, United States, found in a recently concluded double blind random assignment study that THC was superior or equivalent to phenothiazines or butyrophenones. High-dose metoclopramide (2 mg/kg, intravenously, every two hours) was superior to THC (10 mg/m^2, per os, every three hours) in patients receiving chemotherapy for neoplastic diseases. THC showed greater toxicity than standard anti-emetics, but the side-effects were considered manageable. To decrease the side-effects particularly on the central nervous system, it has been suggested that Nabilone and THC be tried in combination with other standard anti-emetics ([8], pp. 163–172).

Another area where cannabinoids have been used for therapeutic purposes is the treatment of glaucoma. J. Merritt of the University of North Carolina described the guidelines for the use of cannabinoids in the therapy of heterogeneous glaucoma. He suggested that patients who responded to cannabis inhalation with significant occular hypotension but without significant effects on the cardiovascular and central nervous systems should be instructed to continue their inhalation as out-patients. Those patients might also add inhalation of cannabis at daily or twice-daily intervals to an ongoing standard glaucoma therapy. Elderly patients with glaucoma should be instructed to sit quietly for 20 to 25 minutes after each inhalation to lessen the chance of orthostatic syncopal episodes. Attempts have been made to develop a topical ophthalmologic formulation for cannabinoids to reduce the risk of adverse effects associated with their long-term use. Unfortunately, research to date suggests that this route does not appear to be efficacious ([2], p. 75).

P. Consroe of the University of Arizona used the rats susceptible to audiogenic seizure as a model of epilepsy to evaluate the anticonvulsant activity of CBD and its analogues. Differential neurotoxicity of these compounds was also assessed. Those studies indicated that the anticonvulsant effect of CBD was not stereospecific, but anticonvulsant effects of CBD analogues might be stereospecific. On the basis of these studies, it is believed that modifications of CBD molecule can yield novel anticonvulsants that are highly potent and efficacious in preclinical tests ([2], p. 69).

THC has been shown to have a weak analgesic effect on several species, including man. B. Martin of Virginia Commonwealth University, United States, noted that as opposed to the subcutaneous route, intravenous administration of THC to mice caused a substantial increase in its analgesic effects. This antinociceptive activity of THC apparently seemed to be independent of the opiate system ([9], pp. 1523–1530). Assessing the analgesic activity of a nitrogen analogue of the cannabinoid assigned as "SP-1" and its derivative Nabitan, H. G. Pars of SISA Pharmaceutical Laboratories, United States, noted that those compounds exhibited potent and long-acting antinociceptive properties when administered via parenteral or oral routes. Oral use of Nabitan showed an analgesic potency six times that of codeine in cancer patients with chronic pain, but at doses of four and eight mg, per os, subjective side-effects were also observed. A new methyl analogue of Nabitan (Menabitan), which was undergoing advance testing, showed greater specificity in analgesic and central nervous system effects in laboratory animals ([2], p. 78).

A number of other scientists contributed to the discussion at the symposium on current cannabis reseach, including Sir W. Paton of Oxford University, United Kingdom; R. Mechoulam of Hebrew University, Israel; M. Braude of the National Institute on Drug Abuse, United States; C. E. Turner of the White House, United States; A. M. Zimmerman of the University of Toronto, Canada; S. Burstein of the University of Massachusetts, United States; and M. R. Issidorides of the University of Athens, Greece.

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