The Psychopharmacology of 'Cannabis sativa': A Review

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Psychopharmacological studies of *Cannabis sativa* (marihuana) have become increasingly abundant in recent years with little time taken for critical review. The following is an attempt to evaluate primarily the behavioural work on this popular drug. A brief discussion of the pharmacology of the drug is also presented for a more total picture of cannabis effects.

Cannabis

The substrates thus far isolated from the *Cannabis sativa* plant include: Δ^8- and Δ^9-*trans*-tetrahydrocannabinol (THC), cannabinol, cannabigerol, cannabichromene, cannabicyclol, cannabidiol, cannabivarin, tetrahydrocannabivarin, cannabidiolic acid, cannabigerolic acid, and Δ^9-THC acid [1, 2]. Note that Δ^8-THC is the same compound as $\Delta^{1(6)}$-THC and Δ^9-THC is equivalent to Δ^1-THC; two numbering systems for these compounds are presently in use.

Δ^8- and Δ^9-THC appear to be the major psychoactive cannabinoids [3–7]. These substances constitute about 1% of the cannabis plant and from 2 to 16% of cannabis extract or *hashish* with the Δ^9-isomer in greater abundance than Δ^8-THC [7–9].

The variable THC content of cannabis plant or extract necessitates chemical assay for THC and other substances prior to its experimental use. Assay is also wise even if THC is used since it decomposes (mainly to cannabinol) under certain conditions. Storage at room temperature under nitrogen, air or acetone with exposure to light results in a substantial loss of THC (to about 12%) after 5 months. Little decomposition occurs even after this time period if THC is kept in darkness at 0° under one of these gases (to about 97%) [10].

Cannabidiol, cannabinol, cannabichromene, cannabivarin and tetrahydrocannabivarin have weak psychoactive properties in mice, rats, cats and dogs [1, 2, 5, 6, 11]. Oddly, antibiotic activity has been reported for cannabidiol, cannabigerol, cannabidiolic acid and cannabigerotic acid [1].

Several synthetic cannabinoids, Δ^3-THC, pyrahexyl, methyloctylpyran (MOP) and dimethylheptylpyran (DMHP), are also psychoactive; the potencies of these compounds are not equivalent to that of Δ^9-THC [12–15].

Metabolic fate of THC

Since THC is the cannabinoid of interest to most investigators, pharmacological studies have concentrated on its action. Of particular interest is whether THC or a metabolite of THC is the psychoactive substrate; how this substance is metabolized by the body; whether the drug acts only on central nervous system tissue or if THC exerts an effect on peripheral nervous tissue as well; and whether the drug alters or influences levels or turnover rates of neurotransmitter substances. The last point is considered beyond the scope of this paper; but there is evidence that THC *(in vivo)* alters levels of norepinephrine, dopamine and serotonin in whole brain preparations [16–20].

In vitro treatment of various mouse tissues with THC indicates that up to 80% of the drug is metabolized by the liver; little if any is metabolized within the central nervous system (CNS) [11]. The major metabolite, isolated from rabbit and rat liver treated with Δ^9-THC, is 11-hydroxy-Δ^9-THC (11-OH-Δ^9-THC) [21, 22]. Similarly, 11-

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OH-Δ^8-THC is the corresponding metabolite of the Δ^8-isomer [11]. Although the metabolic products are more potent than Δ^8- or Δ^9-THC, they exert a similar influence on mouse behaviour [11].

Evidence is accumulating to suggest that the 11-OH metabolites are the psychoactive forms of THC. In the mouse, behavioural effects of THC treatment occur at the time 11-OH THC appears in blood plasma [11]. In addition, studies imply but do not prove that the OH metabolites exert a direct influence on CNS tissue: 11-OH THC has a greater effect when given intracranially (IC) compared to intravenously (IV) but THC has a similar effect whether administered IC or IV with symptoms occurring more rapidly when the drug is given IV [11].

In spite of the apparent action of 11-OH THC on CNS tissue, very little of it or THC reaches the brain (about 0.2% in rats) and most of this amount, 77%, is in the form of Δ^9-THC (in the squirrel monkey) [23–27]. If 11-OH-Δ^9-THC had an exclusive influence on CNS tissue, presumably the radioactive substrate in the brain would be this metabolite rather than unaltered Δ^9-THC.

Radioactivity is detected in most regions of the brain (rat or squirrel monkey) after ^{3}H-Δ^9-THC administration (10 mg/kg IP, rat; 2, 10, 30 mg/kg IV, monkey) [26, 27]. Although intraperitoneal (IP) drug administration in the rat does not yield differential regional distribution of radioactivity in the brain, IV treatment in the squirrel monkey allows THC to concentrate more in some brain areas: in particular, frontal, parietal, striate and limbic cortices, colliculi, geniculate nuclei, corpus striatum, cerebellar cortex, pons and medulla [27].

Systemically, the lungs, liver, bladder, salivary glands and gastrointestinal tract accumulate most radioactivity after ^{3}H-Δ^9-THC treatment (rats) [23–25]. The distribution of radioactive material in the rat is similar whether the drug is given IP, IV or via smoke inhalation but the IP route yields the slowest and most inconsistent distribution [24]. For example, after ^{3}H-Δ^9-THC treatment, radioactivity in brain tissue reaches its maximum amount after 15 minutes with IV treatment and after 1 hour with IP drug administration [26, 27]. Differences in rate of absorption and distribution of THC, according to method of drug administration, should be taken into consideration for evaluation of either pharmacological or psychological studies of the drug.

High concentrations of radioactivity in intestine and bladder indicate that feces and urine are the main routes of drug elimination (rabbit and rat); approximately 80% of the drug (or metabolites) exit via the feces. THC elimination is slow and radioactivity is detectable 7 days post-treatment [23, 24, 28, 29].

THC suffers a similar metabolic fate in man [30, 31]. 11-OH-Δ^9-THC appears in the blood plasma within 10 minutes in humans injected (IV) with ^{14}C-Δ^9-THC (0.5 mg); subjects were either chronic cannabis users or individuals with no previous experience with the drug. About 80% of the radioactive material was collected in the feces and urine over the following 10-day period. Only a small percentage of this (1% of urine and 10% of fecal material) could be characterized as THC or the 11-OH metabolites, however; the rest were unidentified substances. Thus, as in rats and rabbits, THC is metabolized and eliminated by the human body during a period which extends beyond the interval of the intoxicating effects of the drug (rarely more than 8 hours).

The metabolic and subjective responses of chronic cannabis users compared to cannabis non-users in this study were quite noteworthy. Not only did 11-OH-THC stay in the plasma of users twice as long as in non-users, but users eliminated more of the drug via urine. Users also claimed they felt slightly intoxicated by this minute dose (0.5 mg) although non-users were unaffected [30, 31].

Thus, some change and/or sensitization likely occurs in response to repeated exposure to cannabis. This effect offers some substance to anecdotal reports of 'reverse tolerance' to cannabis with its chronic use [32]. That is, when the psychoactive substrate remains in the plasma longer, less cannabis would have to be consumed to maintain a desired level of intoxication.

For the remainder of this review, in the interests of clarity, reports bearing on cannabis effects in humans and infrahumans are discussed separately.

Animal studies

Physiological reactions and general activity level

Cannabis treatment depresses physiological functions and reduces spontaneous activity in most organisms studied; an excitatory phase has been reported for some species, however. Thus, cats, dogs, rabbits, pigeons, rhesus monkeys and

chimpanzees show a depressed reaction to the drug [7, 33–37] but an excitatory period prior to sedation is evident in mice, rats and squirrel monkeys [3, 17, 36, 38–41].

Typical depressed activity is seen in the dog: a decrease in heart rate, drop in arterial blood pressure, depressed respiration, decreased reflexes and ataxia are observed after treatment with THC, cannabis extract or pyrahexyl [6, 14, 16]. In the rabbit, corneal areflexia is sufficiently reliable after THC, cannabis extract or pyrahexyl treatment that it is used as an indicant of the potency of drug samples [15].

Squirrel and rhesus monkeys and chimpanzees show a prolonged (up to 1 week) depressed response to a single high dose of Δ^9-THC (16–64 mg/kg IP; squirrel monkey; 4 mg/kg IP, rhesus monkey; 2–4 mg/kg oral, chimp) [33, 36]; 250 μg/kg (IP) of Δ^9-THC is sufficient to induce akinesia in the rhesus monkey [7]. The depressed response in squirrel monkeys was sufficiently severe in some cases for death to result. It was mainly attributed to respiratory depression and a decrease in food and water consumption [36]. There are no reports to date of a similarly lengthy reaction to one drug treatment in other animals or in humans although lethal doses of THC, pyrahexyl, cannabinol and cannabidiol have been found for mice, dogs, rabbits and guinea-pigs [6].

Excitatory reactions to cannabis are usually contingent on dose or post-treatment time. Low doses of hashish smoke extract (in the mouse) and pyrahexyl (in the rat) yield an increase in activity but high doses evoke a depressed reaction [38, 40, 41]. Others have observed only a progressive sedation with increasingly larger doses of cannabis in mice and rats [42, 43]. LSD-treated rats, too, are more active at lower doses and less so at high doses [44].

In contrast, squirrel monkeys are only sedated by low doses of Δ^9-THC (4–8 mg/kg IP) but show a stimulated period prior to severe depression with higher doses of the drug (16–64 mg/kg) [36]. Moderate doses of Δ^8-THC (2–8 mg/kg IP), however, only stimulate activity in this monkey; higher doses of the Δ^8-isomer were not administered [36]. The differential dose effect of Δ^8- and Δ^9-THC in these monkeys was surprising since the Δ^8 isomer is considered to be less potent than the Δ^9-one [3].

Cats, too, can be stimulated by moderate or high doses of Δ^9-THC (1 or 4 mg/kg IP) but this observation is best explained as a case of individual differences in drug reaction. Only two out of six cats showed this reaction; the rest were sedated by all doses of Δ^9-THC (0.5–4 mg/kg) [35].

Hungry rats show a time-dependent cannabis reaction (extract: 30–150 mg/kg IP). At first they are excited and hyperactive; inactivity and ataxia eventually set in. Onset of the second phase occurs more rapidly with larger doses [43].

Electrophysiological reactions

Electroencephalographic (EEG) changes induced by THC treatment also vary according to drug dose. Chronically prepared rabbits and rats show low voltage fast (LVF) activity interspersed with a hypersynchronous pattern after THC treatment (Δ^8- or Δ^9-THC: 0.5–1.0 mg/kg IV, rabbit; Δ^8-THC: 20 mg/kg IP or Δ^9-THC: 10 mg/kg IP, rat) [5]. Higher doses (up to 10 mg/kg) of Δ^8- or Δ^9-THC, in the rabbit, yield continuous spike and wave activity (without overt convulsions).

Comparable EEG patterns are observed in acute rabbit preparations treated with Δ^9-THC (0.5–1 mg/kg IV) [5] while higher doses of Δ^8- or Δ^9-THC (8 mg/kg IV) in this preparation create only increased LVF activity [45].

A similar dose-response relationship occurs in the chronically prepared cat: synchronized high voltage activity appears with a low dose of Δ^9-THC (0.5 mg/kg IP) but is increasingly interspersed with LVF activity at a higher dose (4 mg/kg IP) [5, 35]. Interspersion of synchronized activity with LVF action is a typical EEG response to hallucinogenic substances (e.g., mescaline, psilocybin and LSD) [46].

LVF activity in the cat can be elicited even at lower doses of THC (2 mg/kg), however, if the animal is presented with a novel stimulus [5]. The hypersynchronous activity of LSD-treated cats is blocked after mild external stimulation as well [47].

The cortical response to stimulation of the brain stem reticular formation (BSRF) is also influenced by cannabis treatment but reports of this phenomenon conflict. Two teams indicate that Δ^9-THC or DMHP abolishes the electrocorticographic (ECoG) desynchronization response elicited by BSRF stimulation (cat) [5, 48]. Others claim THC *lowers* the threshold for the ECoG response to BSRF stimulation (rabbit) [45]. Although no dose-effect relation emerges to explain the difference, species differences could be involved.

Interestingly, the cortical response to stimulation of the intrinsic thalamic nuclei is not altered by DMHP in the cat suggesting that this THC homologue has a particular effect on the brain stem portion rather than the thalamic part of ascending reticular pathways.

The activity of descending pathways is also influenced by THC homologues. DMHP- or MOP-treated cats with midbrain section, high spinal section (Cervical 1) or low spinal section (Thoracic 12) show a revealing pattern of spinal reflex responses: low spinal cats have depressed reflexes above the section as do intact animals given DMHP or MOP; no depression of spinal reflexes is seen in high spinal animals; but reflex suppression occurs after midbrain transection in drug-treated cats (12). As suggested above, the area between the first cervical vertebra and the midbrain, the lower brain stem, is particularly sensitive to THC homologue action.

Considering descending brainstem pathway responses to the THC homologues as well as the cortical responses to brain stem stimulation, it would be of interest to known how brainstem transections at various levels alter cortical responses to THC or its homologues.

Dominance and aggression

Reduced aggressiveness frequently accompanies the hypoactivity observed with cannabis treatment. Rhesus monkeys, for example, are quite tame after THC treatment [7]. The aggression of the 'fighting mouse' is also quelled by THC or pyrahexyl [42, 49, 50]. A fighting mouse attacks any mouse introduced into its cage.

Conversely, increased aggressiveness is observed in hyperactive cannabis-treated rats deprived of food. The reaction is more pronounced in the female [51, 52].

Aggressive or dominant behaviour is not only related to hyperactivity or hunger; rats treated with THC also show increased aggressiveness toward untreated rats in a food competition. The phenomenon may be task-specific, however, as it occurs in a simple straight alley but not in a *T*-maze [53]. Since the latter situation allows exploration and distractions (blind alley), the authors concluded that perception of the environment rather than an increase in hunger or activity, plays a crucial role in eliciting dominant behaviour in rats. Similarly, mescaline, considered to reduce dominance in a competitive situation in rats, also increased winning (dominant) behaviour in a straight alley task [53].

Learning

Even a simple learning situation such as habituation to an unfamiliar place can be disrupted in mice by cannabis treatment [54]. Habituation was measured as the latency to begin drinking in a chamber previously entered while under the influence of Δ^8-THC (0.32–3.2 mg/kg IP). THC-treated mice showed a longer latency than untreated controls indicating that the habituation process was attenuated by the drug; the effect was blocked by the administration of tacrine, an anticholinergic antagonist. Other anticholinergic drugs (e.g., scopolomine, atropine) also disrupted habituation to the chamber in mice [54].

Learning based on negative reinforcement is also adversely affected by cannabis treatment; extinction of an avoidance response (jumping onto a platform) and shuttle box avoidance learning are hindered by treatment with hashish smoke extract (25 mg/kg IP) [41], cannabis extract (62.5, 125 mg/kg IP) [55] or Δ^9-THC (7.5 mg/kg IP) [56]. The less potent Δ^8-THC (15 mg/kg IP) produced only a small (but non-significant) impairment in acquisition of a shuttle box avoidance response [56]. Poor avoidance learning after cannabis or THC could not be blamed on drug-induced analgesia since experimental and control rats had indistinguishable response latencies to shock [56].

Although acute treatment with a small dose of cannabis extract (10 mg/kg IP) failed to disrupt avoidance learning in rats, impaired avoidance learning occurred if the rats were given this dose for 23 days and trained on the 24th day [52]. The observed deficit was interpreted as a cumulative drug effect. This conclusion gains support from metabolic studies, discussed above, which indicated that THC is eliminated quite slowly and therefore could accumulate in sufficient amounts to mimic acute treatment effects [30, 31].

Positively motivated maze learning (Lashley III maze) is influenced by cannabis treatment (extract: 10 mg/kg IP) as well but this dose either induced rats to run faster and to make fewer errors [43] or to run slower and to make more errors than controls [52]. Despite divergent results, both studies observed hyperactivity and aggressiveness in their cannabis-treated rats. Note that this relatively small dose of extract (acute treatment) failed to disrupt avoidance learning in rats [52].

Methodological differences between these two maze learning studies can account for the opposing outcomes if one considers such vari-

ables as the delay between injection and testing and the extent of exposure to the drug, points that ought to be noted in all psychopharmacological studies. The first study's rats [43] began training only 3 minutes after cannabis injection and were run and injected every other day for a total of fourteen trials (28 days); improved performance appeared after trial seven (sufficient time, perhaps, for cannabis tolerance to have developed). The second investigation in question [52] began training 15 minutes post injection and trained animals daily for eight trials (8 days). Thus faster maze learning [43] may be associated either with an initial phase of excitement that occurs immediately after cannabis injection or with the development of tolerance to the drug's sedative and slowing effects.

The precise manner in which cannabis influences learning is far from clear. One study casting doubt that the drug influences the consolidative aspects of learning should be mentioned. Cannabis extract (10 mg/kg) and strychnine were compared in their effect on consolidation of a maze learning task [57]. Even though both drugged groups learned the task faster than controls when the drugs were given prior to the trial, only strychnine had the same effect when given immediately after the trial, suggesting that this substance indeed influenced consolidative processes involved in learning this task. The increased rate at which cannabis-treated rats learned was considered a consequence of a general effect rather than a specific one on consolidation. Note that Carlini and associates are the only investigators to observe faster maze learning in cannabis-treated rats.

Some of the following work on learned performance also indicate that cannabis's main influence is as a general (activity) effect.

Learned performance

Performance decrements on previously learned tasks are frequently encountered with acute cannabis treatment. Prolonged or chronic treatment, however, alleviates many behavioural symptoms. Consequently, studies involving acute and chronic cannabis treatment will be examined separately.

Acute studies. A decrease in motor activity (akinesia) and/or reduced motivation due to hypophagia plausibly explain some performance deficits induced by acute cannabis treatment. Pigeons, rats and chimpanzees, sedated by cannabis, performed fixed ratio (FR), fixed interval (FI) or multiple FR-FI schedules of reinforcement at reduced rates after Δ^9-THC treatment (0.3–3 mg/kg IM, pigeon; 3–18 mg/kg IP rat; 3–4 mg/kg oral, chimp) [34, 38, 39]. Response rates were inversely related to drug quantity.

The decrease in response rate was not accompanied by impaired visual discriminative ability. Pigeons treated with cannabis extract (20–30 mg/kg IM) made accurate colour and form discriminations [37] and pigeons, rats and chimps on multiple schedules of reinforcement used visual cues to differentiate accurately among schedules [34, 58, 59]. Interestingly, pigeons, given a dose of LSD that produced a decrease in response rate comparable to that obtained with cannabis, were deficient in a colour and form visual discrimination task [37]. Auditory discriminative abilities have not been tested during cannabis treatment.

Temporal discrimination performance is disrupted by cannabis, however, and occurs with both a positively reinforced DRL schedule (differential reinforcement for a low response rate) or a negatively reinforced continuous (Sidman) shock avoidance schedule. In the former situation, the subject must wait a specified amount of time between responses in order to obtain food or water and for the latter, a predetermined interval must elapse between responses for efficient shock avoidance. Disruption of 'time estimation' is most clearly evident if low or moderate doses of cannabis are used; high doses usually result in only a cessation of bar pressing.

A pattern of response similar to that induced by hallucinogenic drugs is observed in THC-treated rats (0.75–9 mg/kg IP) performing a Sidman avoidance schedule: an increase in both early and late responding with the former predominating [60]. The former type of response delays shock but is an inefficient response while the latter is made to escape from ongoing shock.

A variety of disrupted response profiles was observed in rats trained to perform a DRL schedule (Δ^9-THC: 1.5–9 mg/kg IP): complete cessation of responding (most cases), long pauses between bursts of responses, a slower but continuous response rate or an increased rate of response [60]. Mescaline and amphetamine yielded more consistent effects; the former caused long pauses between bursts of evenly spaced responses and the latter simply decreased the interresponse time [60].

The temporal error of rats in both the Sidman avoidance schedule (the tendency to overestimate time passage and thus to respond too early) and the DRL schedule (short interresponse times mixed with long pauses) is similar to that observed in humans (see below) and chimpanzees. The impairment for the latter type of primate was evident for a DRL schedule (THC: 1–2 mg/kg oral) and was inferred by significantly short interresponse times mixed with long periods of no response [58]. The schedule was part of a multiple FR-DRL-Time Out schedule.

Although 1 or 2 mg/kg of THC was sufficient to disrupt DRL performance, it did not affect FR schedule response rates; higher doses (3–4 mg/kg oral) were needed for that effect. The degree of response suppression during the time out period was too variable under both drug and control conditions to establish a reliable effect [58].

A more complex temporal discrimination also indicated overestimation of time (decreased interresponse time) as a cannabis-induced error (THC: 0.25–2 mg/kg oral) [33]. Here, chimps not only waited a specified amount of time before responding but then had to respond within a time limit for the correct completion of a trial. This situation was particularly complicated since reinforcement was contingent on completion of 500 successively correct trials.

Tests of short term memory, a delayed matching and a delayed oddity test, also isolate cannabis-induced behavioural impairments. Rhesus monkeys, trained to puff cannabis cigarettes (the monkeys had access to 30 cigarettes containing about 0.75 mg THC each), were significantly less accurate in a delayed matching test when a 30-second delay was in effect; the impairment was not as great with shorter delays [61].

Similarly, monkeys made more errors in a delayed oddity test, in which they indicated, after cannabis treatment (THC: 0.5–2 mg/kg oral), which stimulus light did not match a sample light [61]. Si multaneous presentation of sample and response stimuli, however, did not yield a deficit in cannabis-treated monkeys.

Accuracy was diminished in the delay tasks at all doses with impairment being most severe after a high drug dose. Response rates were reduced as well on both tests with the degree of suppression proportional to dose. Although a slower response rate was attributed to a lack of motivation, akinesia may have contributed to this effect.

Presumably, disordered short term memory, induced by cannabis, also contributed to deficits in temporal discrimination performance mentioned above. Note that impairments in short term memory and temporal orientation are frequently observed in humans intoxicated by cannabis.

Chronic effects. Although rope climbing and various positively reinforced operant tasks are disrupted when rats are first given cannabis extract (10 or 20 mg/kg), the deficits are completely eliminated after as few as seven daily treaments with the drug [39, 62].

Pigeons on FI or FR schedules of reinforcement regained their baseline rates of pecking after 13 days of THC treatment (1.8 mg/kg IM) [63]. Pigeons can also maintain baseline rates of pecking with increasingly larger doses of THC (i.e., from 1.8 mg/kg to 36 mg/kg over 27 days). The smallest dose completely suppressed pecking at first and drug-naive birds given only 36 mg/kg of THC were severely ataxic [63].

Physiological dependence to THC was not apparent here since performance did not change when drug treatment was terminated. Nonexperimental reports for humans also indicate that no physical symptoms develop after discontinuation of chronic cannabis use although psychological dependence is often reported [64, 65].

Although the pecking rate of pigeons tolerant to Δ^9-THC did not change following withdrawal of the drug, performance of rats on a shuttle box avoidance task, learned during chronic drug treatment, did suffer when cannabis was withheld (Δ^9-THC: 7.5 mg/kg IP) [56]. Since the converse situation yielded similar results, i.e., training before cannabis exposure and testing during chronic cannabis administration [52, 56], it was inferred that cannabis, like a variety of CNS depressant drugs, induces state-dependent learning [56].

In spite of the ease with which behavioural tolerance is established with chronic cannabis treatment, physiological symptoms of cannabis use do not similarly diminish during long term drug administration. For example, the hypophagia seen in rats treated with Δ^9-THC was not alleviated during a 30-day period of chronic drug treatment [66]. And, EEG patterns associated with THC treatment in cats did not return to a predrug pattern with chronic treatment [5].

In most studies of learning and performance, cannabis induced deficits could have resulted from a change in activity level. The only task

types that adequately dissociated slow performance from other cannabis effects were those requiring intact short term memory and accurate discriminative ability (sensory and temporal) since deficits were evident even when the response rate was at the predrug level.

Performance of such tasks has been studied only after acute cannabis treatment. It would be of interest to see if deficits in short term memory or temporal discrimination tasks would diminish under chronic cannabis treatment. This question is particularly intriguing since in most chronic treatment studies, alleviation of behavioural symptoms could be parsimoniously explained as a return of motor functions to a predrug level and since in acute treatment studies, motor deficits need not occur concurrently with memory or timing impairments.

Human studies

Physiological effects

Human responses to cannabis have both excitatory and depressive components. Thus an increase in pulse rate, tachycardia, reddened conjunctivae, ptosis, nausea, an increase in urine output, general relaxation, weakness, sleepiness and ataxia (at very high doses) are common reactions to cannabis consumption [32, 67–69]. A small but significant drop in body temperature after THC ingestion has also been reported [70]. These effects contrast with those of LSD and other hallucinogens which are more consistently sympathomimetic: tachycardia, pupil dilation, increased blood pressure, hyperreflexia and an increase in body temperature [71].

The EEG of the cannabis-treated human also differs from its normal pattern; longer intervals of low voltage fast activity with a decrease in incidence of alpha waves are frequently observed after cannabis intake [4, 67]. This pattern, somewhat similar to the EEG of cats treated with THC, is comparable to the EEG tracings of humans treated with LSD [71].

Physiological symptoms of cannabis consumption occur irrespective of an individual's past experience with the drug [4]; a situation in marked contrast to the interaction of previous drug experience with the behavioural and subjective effects of cannabis. Recall that chronic cannabis treatment in animals yielded different behavioural and physiological outcomes as well.

Subjective effects

Alterations in mood induced by cannabis intoxication range from mild euphoria to psychotomimetic reactions. Individual differences in personality, physical make-up, previous exposure to the drug, and dosage presumably contribute to the idiosyncratic subjective effects of cannabis [67, 72, 73].

The euphoric reaction is usually accompanied by drowsiness, a feeling of heavy limbs, dizziness, a sense of self-confidence and well being, depersonalization and temporal disorientation [67–70, 74]. Distortion of time is usually manifested as a tendency to overestimate time passage [4, 32, 75–77).

A dysphoric effect, related mostly to somatic discomfort (especially nausea) induced by the drug, occurs occasionally after ingestion of cannabis and is a transient phenomenon [4, 70, 72].

Keener auditory and visual perception is often reported but there is no experimental evidence that visual or auditory thresholds or discriminative abilities change after cannabis intake [78, 79].

The subjective mood changes induced by cannabis are quite similar to those induced by LSD. A questionnaire of subjective drug effects that differentiated LSD-induced symptoms from those of amphetamine or placebo effects also distinguished between THC and placebo symptoms [70]. Although overlap between LSD and THC subjective symptoms was great, such effects as visual hallucinations, feelings of paranoia and panic over possible loss of bodily control were only infrequently reported after THC treatment [69, 70, 72]. Cannabis effects were also considered to be much milder than those produced by LSD [64, 80].

In spite of similar mood changes, there is no cross-tolerance between cannabis and LSD or mescaline [81]. Cross-tolerance among hallucinogenic drugs, however, can be demonstrated [82]. Rats show no cross-tolerance between THC and hallucinogenic drugs as well [62].

The sedative effects of cannabis, on the other hand, are comparable to those observed during ethyl alcohol intoxication but subjects can easily distinguish between ethanol and cannabis effects [4, 76]. Cross-tolerance between cannabis and alcohol has been inferred for humans [4] and experimentally observed in rats [83].

Although cross-tolerance between ethanol and cannabis may occur, the effects of these drugs do not interact. Rather an additive effect is observed when the two are taken simultaneously [84]. That is, the deficit observed when subjects

(human) were given both alcohol and THC was greater than that seen when only THC was given, but the slopes of the dose-response curves were the same. The additive effect held for both physiological measures (pulse rate, somatic symptoms) and psychological ones (pursuit rotor task, reversed verbal reading with delayed auditory feedback).

The above comparisons indicate the elusive quality of cannabis in terms of pharmacological classification. Apparently, it cannot be glibly considered to be an hallucinogen, in spite of some similar mood changes induced by both types of drugs. The sedative properties of cannabis and its cross-tolerance with ethanol implies that cannabis could be a depressant drug, but most subjective effects of these drugs are not comparable. Experimental behavioural studies add little clarification to this question, as will be seen, since cannabis effects bear some similarities to those of both hallucinogens and depressants.

Experimental studies

When assessing the behavioural effects of cannabis in human subjects, a number of methodological variables must be considered. They include: form of cannabis, dosage, method of administration, the previous experience of the subject with cannabis and this expectation of effect. New permutations of these variables seem to appear in each study. Although some factors are relevent to infrahuman work, they gain particular significance when humans are subjects.

The Table contains data from recent major studies of the behavioural consequences of cannabis in human subject, and summarizes the variety of experimental conditions used in this area of research. Note that the dose of THC in smoked cannabis refers to the calculated or assayed absolute amount of THC in the plant or extract rather than the amount actually consumed.

A dilemma facing the experimenter is whether to give subjects dried cannabis, its extract or THC. Although administration of THC insures accurate quantification of the theoretically most psychoactive ingredient of cannabis, use of an extract (that usually contains at least cannabidiol and cannabinol) or cannabis plant has certain advantages. Each contain other substrates that might subtly potentiate THC effects. Choice of drug form, then, depends on whether one is interested in the effects of cannabis *in toto* or just THC.

Method of drug administration creates another problem. Ingestion and inhalation are the most popular human methods of cannabis intake. The former method creates more somatic discomfort and dysphoria. Dosage and onset of effect could be influenced by stomach content and rate of absorption (controlled by fasting to some extent). The inhalation method has drawbacks as well since the drug is often given with tobacco and dosage is dependent on the smoking efficiency of the subject. Even under ideal conditions, only 50 % of the THC in a cannabis cigarette actually reaches the lungs of the subject [85].

Since dose-response relationships are reported in both animal and human experiments (e.g. [60, 77]), studies that use only one dose of the drug cannot reasonably assess the range of cannabis effects. In addition, dosage is not held constant in some studies; a standard dose is used rather than one based on each subject's weight.

Variation in subjects' experience with and expectation of the effects of cannabis intoxication can also confound experimental results; a problem of less importance in research with hallucinogens. This variable can be controlled to a limited extent by using subjects with similar exposure to the drug and a number of experiments have screened subjects in this way. Even so, placebo effects for the subjective changes in mood, in particular, are quite variable. Also, under some conditions, experienced users show behavioural profiles that differ widely from those of drug-naive individuals [32, 84].

Placebo effects are particularly evident when cannabis is smoked rather than ingested although both methods yield similar behavioural and physiological effects [4]. Both experienced users and drug-naive individuals have difficulty distinguishing between some of the subjective effects induced by placebo (THC-free cannabis) and unadulterated cannabis cigarettes but the effect is most evident for the experienced user [4, 32, 84].

Apparently, many subjective effects are learned or influenced by expectation. However, it is also likely that the dizziness and lightheadedness associated with euphoria are evoked by the deep inhalation and breath-holding required when smoking cannabis. Possibly, in addition, placebos that are THC-free cannabis contain cannabinoids that induced feelings associated with intoxication.

In spite of their susceptibility to cannabis-induced subjective mood changes, experienced cannabis users are able to compensate for some drug-induced behavioural impairments. For example, experienced users, administered cannabis, performed the digit symbol substitution test better than drug-naive subjects given a placebo and much better than naive subjects treated with cannabis [32]. Unfortunately, the study did not include experienced subjects tested under placebo conditions. The Mayor's Report of 1944 [74] also reported that cannabis users, when given the drug, showed less deviation from their no-drug level of performance on Bellevue IQ subtests than individuals introduced to the drug for the first time in the experiment.

That subjects familiar with cannabis experience different behavioural consequences of cannabis treatment than drug-naive individuals presents a serious problem for experimenters. Apparently, users and non-users of cannabis should be considered as two different subject populations.

Behavioural tolerance or learned methods for overcoming deleterious behavioural effects of cannabis may aid the experienced cannabis user to circumvent his behavioural reaction to the drug. The inexperienced subject, conversely, may be anxious about the psychological and physical effects of this popular drug that he has never tried informally and would be alarmed and/or distracted by his reaction to cannabis. Obviously, comparisons between the psychological responses (both objective and subjective) of drug-naive subjects and those who have had some experience with cannabis need to be made.

Despite diverse experimental conditions, some reliable behavioural effects of cannabis have been obtained. The laboratory setting, of course, is not the same as the informal social situations in which the drug is usually consumed, although some studies have attempted to mimic a non-experimental environment by playing music or by otherwise assuming an informal atmosphere. Nonetheless, the experimental findings should be considered as approximations of cannabis effects that occur in the world outside the lab.

With this cautionary note in mind, experimental investigations of cannabis effects will be examined. For the most part, these studies have attempted to assess sensory-motor coordination, perceptual processes, memory and problem solving ability.

Sensory-motor performance

An early exhaustive study of the behavioural effects of cannabis extract, the Mayor's (New York City) Report of 1944 [86], found that certain motor tasks (static equilibrium, hand steadiness and complex reaction time) were adversely affected by cannabis. Time and distance estimation, tapping and simple reaction time were not impaired by the drug unless a large dose was consumed. This study has been criticized for use of uncertain doses and inadequate placebos. Later studies have attempted to overcome these problems as well as add new information.

Recent investigations are in general agreement with the Mayor's Report. They indicate, for example, that cannabis-produced impairments are evident in complex tasks that require rapid decisions and quick movement. Thus, cannabis extract or THC does not affect depth perception [79], field dependence as measured with the rod and frame test [4, 76], or mirror image tracing [79] but does impair complex reaction time and continuous tracking performance [32, 79, 85].

In view of these findings, a surprising claim made recently is that automobile driving remains unimpaired during cannabis intoxication [87]. Experienced cannabis users were found to be proficient in most aspects of driving after smoking cannabis but were grossly impaired in all aspects of the task after drinking ethanol (e.g., braking, accelerating, signalling and steering).

The study has been criticized on a number of points, however. Control subjects were not given a placebo; they merely rested while others were administered the drug. Driving ability was assessed in a simulated situation rather than on the road in an automobile. Finally, subjects were not given a regulated dose of cannabis but smoked it until they 'felt' intoxicated (note that experienced users may require very little drug to reach this state and apparently can overcome some deleterious cannabis effects [31, 32]).

Cognition

In addition to deficits in rapid complex performance, certain cognitive functions are particularly affected by cannabis. Tasks employing parts or adaptations of widely used memory and intelligence tests indicate that short term or recent memory is impaired by cannabis but that other cognitive abilities that rely on long term memory and complex integrational processes are not particularly influenced by cannabis intoxication.

Major experimental studies with human subjects.

Study	Drug form	Route	Dose	Drug vehicle	Placebo effect	Subjects
Abel [89]	cannabis	smoke	2 cigarettes	cannabis	no placebo	normal adults cannabis users
Clark et al. [75, 79]	extract	oral	0.125, 0.2, 0.3 mg/lb THC	ethanol capsules	?	cannabis-naive male students
Crancer et al. [87]	cannabis	smoke	1.7 g cannabis	cannabis	no placebo	cannabis users normal adults
Halpern [74], Morrow [86]	extract	oral	2–5 cc	glycyzzhiza capsules	no placebo	male and female prisoners
Hollister et al. [68]	THC pyrahexyl	oral oral	30–70 mg 50–200 mg	ethanol drink	no placebo	normal males
Isbell et al. [69]	THC	oral	0.12 mg/kg	ethanol drink	?	former opium addicts, male
		smoke	0.05 mg/kg	tobacco	?	
Jones and Stone [4]	cannabis extract	smoke oral	4.5 mg THC 90 mg THC	cannabis tragacanth capsules	yes no	normal males cannabis users
Manno et al. [84, 85]	cannabis	smoke	5, 10 mg THC	cannabis	yes	cannabis-naive male students
Melges et al. [72, 77]	extract	oral	20, 40, 60 mg THC	ethanol drink	no	male students
Waskow et al. [70]	THC	oral	20 mg	ethanol drink	no	male prisoners
Weil et al. [32]	cannabis	smoke	4.5, 18 mg THC	cannabis	no	cannabis-naive male students

Impairments, if found, occurred regardless of previous experience with cannabis (see Table).

Performance on tests of short term memory, successive addition and subtraction and digit span, was hindered by cannabis treatment [70, 77]. Proficiency on these tests was impaired in a delayed auditory feedback situation after cannabis treatment as well [84, 85]. The latter paradigm yielded similar deficits with ethanol intoxication [88].

Immediate memory for ideas and content of verbal passages presented orally [89] or visually [75] was adversely affected by smoking cannabis as well. Although experimental subjects made as many responses as non-intoxicated controls, the recalled material of the former group contained more erroneous statements [89]. Similarly, verbal expression was distorted and disoriented in cannabis-intoxicated subjects with illogical thinking, inability to keep a train of thought and remote associations commonly observed [90].

Performance on the digit symbol substitution test, which pits learning and memory against fast accurate performance, can be impaired by cannabis if a large dose is given [4, 32, 79]. The test is not too helpful for pinpointing a cannabis-induced impairment, however, since either motor slowness or impaired memory and learning result in a low score. A performance decrement on the digit symbol substitution test is also observed in LSD- or barbiturate-treated subjects [91].

Integration of information and recall have been tested (without an interacting performance effect) with anagram problems. Intoxicated subjects can solve such puzzles but are unable to remember their solutions (words) immediately after the session (while still intoxicated) [89]. Recall but not information processing, presumably then, is most affected by cannabis treatment.

In contrast, simple tests of long term memory, recitation of the alphabet or a series of numbers (e.g., 20–1) do not reveal any deficits in cannabis-treated subjects [70, 77].

Observations of impaired recent memory is commensurate with findings of cannabis-induced temporal disorientation. In addition, a short term memory disorder may contribute to impairments in complex motor tasks since an inability to quickly remember contingencies for response would slow performance.

Chronic cannabis use in humans

The effects of cannabis cited above involved acute treatment. Direct extrapolation of these effects to those that might appear under chronic treatment should not be done since: it is known that chronic use of the drug can influence behavioural responses to it; human cannabis users metabolize THC differently than non-users; and chronic cannabis treatment in animals yields a different behavioural profile than acute drug administration.

Only one experimentally controlled study of chronic cannabis treatment in humans has been found in the literature. This work is so recent that only a preliminary report of general findings is available [92].

Male volunteers, with previous cannabis experience, were maintained in a quasi-normal but restricted environment for 3 months. They were able to work for food, luxuries and post-experimental money and were given (or allowed to 'buy') THC-free cannabis cigarettes, a mandatory dose of cannabis or *ad lib* cannabis.

Tentative observations of this study were that: no permanent behavioural, intellectual or mood changes occurred with chronic exposure to the drug; reduced work output occurred only with mandatory intake of high doses of cannabis (30 mg) but tolerance to this effect developed; and ad lib treatment did not yield a loss of productivity. Interestingly, prolonged use of a large dose of cannabis (30 mg) was aversive; subjects threatened to quit the experiment under this regimen. Under *ad lib* conditions, cannabis was consumed in only small quantities.

This work, although not completely analysed, suggested that chronic use of cannabis does not have any long term behavioural or psychic effects. It is possible, however, that 3 months was not long enough for any permanent effects to emerge.

Summary and conclusions

This review has attempted to cover major investigations of the psychopharmacological effects of *Cannabis sativa*. A few general points emerge from this plethora of observations:

(1) Tetrahydrocannabinol (THC), the major psychoactive ingredient in the cannabis plant, likely exerts its effect through a metabolic product, 11-hydroxy-THC.

(2) THC or metabolites distribute to almost all parts of the body with elimination of the substance taking far longer than the period of its physiological or psychological effects. Chronic use of cannabis, in addition, alters the metabolic response to the drug as well as the pattern of cannabinoid elimination.

(3) A general depression in physiological functions and activity is a typical effect of cannabis treatment. The degree and duration of sedation not only is species specific and dose-related, but also is dependent on individual differences in sensitivity to the drug. A biphasic effect, with excitation preceeding sedation occurs in some species. Physiological effects of the drug also indicate that cannabis is not a sympathomimetic agent.

(4) THC or homologues exert an (undefined) influence over the brain stem reticular formation. Transection studies imply an effect over descending pathways from the brain stem but only stimulation threshold studies point to cannabinoid action on ascending pathways.

(5) It is not clear whether learning in animals is particularly affected by cannabis; most learning or performance decrements or enhancements likely mirror a general activity effect.

(6) Certain short term memory and temporal discrimination tasks do indicate, however, that recent memory and time estimation are impaired in animals treated with cannabis.

(7) In animals, behavioural tolerance but not physiological tolerance is induced by prolonged cannabis treatment. The tasks used to demonstrate this phenomenon have a dominant motor component, however. The determination of behavioural tolerance with tasks dissociating akinesia from other cannabinoid effects needs to be made.

(8) Akinesia is also implicated in some performance deficits in humans given cannabis. Task complexity and the requirement of a facile recent memory (which is frequently impaired by cannabis) interact in many tasks assessed so far.

(9) Although the physiological effects of cannabis in humans differ to a large extent from the effects of LSD, there is a remarkable similarity in their psychic effects. However, cannabis effects are generally milder than those produced by the hallucinogens: euphoria is more evident and lasts longer and hallucinations rarely occur with cannabis treatment. The sedative properties of the drug, in contrast, are similar to those observed with ethanol intoxication.

(10) Cross-tolerance between cannabis and hallucinogens has not been established; this contrasts the cross-tolerance seen among the hallucinogens. There is some evidence, however, that cross-tolerance occurs between ethanol and cannabis. More studies comparing these drugs should be conducted.

(11) Human reactions to cannabis must be viewed in the context of previous drug experience as well as expectations of cannabis effects. These and other methodological problems such as quantification of dose, method of drug administration, type of placebo, and the influence of experimental setting on drug effects need more careful scrutiny.

(12) Results of chronic treatment with cannabis do not indicate that the drug induces long term behavioural or psychic deficits. Paradoxically, long term use of cannabis yields tolerance to initial behavioural (motor) impairments but 'reverse tolerance' or sensitivity to its psychic and physiological or somatic effects.

This summary has indicated the major properties of cannabis as well as some of the larger gaps in our knowledge about the drug. The wide variety of effects that cannabis can produce as well as the methodological inconsistencies among studies prevent a cogent conclusion about either the pharmacology or psychology of the drug.

Classification of the drug is also elusive. Evidently the drug cannot be glibly considered as an hallucinogen. Many of its action are comparable to those of the psychotomimetics but other effects of cannabis point to its similarity to sedative drugs. Perhaps it would be best to treat cannabis as a distinct psychoactive substance until more substantial information is obtained.

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