Psychotomimetic Drugs: Biochemistry and Pharmacology

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1 Introduction and classification

The term psychotomimetic is not an entirely satisfactory one for the drugs which will be discussed in this review. The implication that the drugs produce effects which are analogous to those observed in naturally occurring psychoses is now generally accepted as being ill founded. It is, however, difficult to find a more satisfactory alternative term though many have been proposed. If the inadequacies of the term are accepted it is necessary to use a precise definition of the drugs and their effects. That produced by Downing in 1964 is very satisfactory. It defines psychotomimetic drugs as substances which will consistently produce changes in thought, perception, and mood, occurring alone or in concert, without causing major disturbances of the autonomic nervous system or other serious disability. This definition stresses the specificity of the drugs and the reproducibility of their effects.

The fact that all the drugs to be discussed here conform to this definition should not be taken to imply that they all possess a common mode of action or that they all produce the same effects. Evidence will be presented to indicate that different groups of drugs have different modes

of action and it is clear that the effects they produce bear only very general and superficial similarities to one another; definite detailed differences exist.

It would be impossible in an review of this length to give anything like a full account of all psychotomimetic substances. The approach adopted here will be to take a relatively small number of drugs from each group and to discuss their pharmacology and biochemistry in some detail. This entails making the assumption, which may not be entirely justified, that all members of the group have identical or similar pharmacological and biochemical actions. In most cases it is not possible to judge the validity of this assumption since only relatively few psychotomimetic drugs have been subjected to detailed studies.

Since so few psychotomimetic drugs have been studied in detail and since even with these there is still considerable ignorance concerning their mode and site of action, any classification of the drugs must be only tentative. At the present state of knowledge the best classification seems to be: (a) sympathomimetic amines—indoleamines, phenylalkylamines and lysergic acid derivatives; (b) antiacetylcholine drugs; (c) cannabis and cannabinoids; (d) miscellaneous.

These groups will be discussed in turn. No mention will be made of the miscellaneous group since this contains a heterogeneous collection of substances bearing no apparent chemical or pharmacological relationships to one another and with modes of action which are not at all understood.

2 Sympathomimetic amines

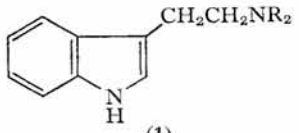
2.1 INDOLEAMINES

It has been stated (Robinson, 1968) that indole-containing compounds comprise about a quarter of all known naturally occurring alkaloids. Many of them have been shown to be psychotomimetic drugs and are responsible for the effects of various fungi and higher plants which have been used by primitive people for many centuries in their religious rites and rituals.

Brown (1971) divided the psychotomimetic indoles into three main groups: the simple indolealkylamines; the β-carbolines; and the iboga alkaloids. Lysergic acid diethylamide (LSD-25) does not occur naturally and is therefore considered separately. Brown's classification will be used here.

2.1.1 *Indolealkylamines*

The simplest psychotomimetic indolealkylamines are *N,N*-dialkyltryptamines (3-(2-dialkylaminoethyl)indoles), (**1**).



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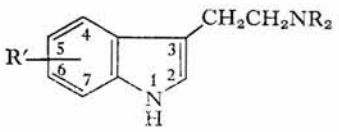
Tryptamine itself (**1**, R = H) exhibits no psychotomimetic activity (Sjoerdsma *et al.*, 1959) but its simplest dialkyl derivatives, *N,N*-dimethyltryptamine (**1**, R = CH_3), *N,N*-diethyltryptamine (**1**, R = C_2H_5) and *N,N*-dipropyltryptamine (**1**, R = C_3H_7), show such activity; the first of these is one of the active principles of cohoba, a snuff prepared from the seeds of species of the shrub *Piptadenia* (Mimosaceae) by Indian tribes in South America and on the Caribbean islands (Downing, 1964).

Tests on human subjects (Sai-Halász, 1962) showed that intramuscular doses of between 0.75 and 1 mg/kg of *N,N*-dimethyltryptamine produced an intense hallucinatory state, rapid in onset and persisting for about 40 minutes. Rosenberg *et al.* (1963) confirmed the effectiveness of a dose of 0.75 mg/kg, although in their subjects the appearance of effects was delayed (15–30 min) and they persisted rather longer (1–2 h). In both these studies hallucinations, perceptual disturbances and anxiety were reported in the subjects. Interestingly, the closely related *N,N*-diethyltryptamine at a similar dose level of 1 mg/kg has been reported as producing longer-lasting (*ca.* $2\frac{1}{2}$ h) and qualitatively different effects with the development of a pleasant, meditative euphoric state (Boszormányi *et al.*, 1959). Also effective in man at about the same dose level are the *N,N*-dipropyl and *N,N*-diallyl (**1**, R = allyl) compounds (Szára and Hearst, 1962). With increase in alkyl chain length there is loss of activity, with *N,N*-dibutyltryptamine (**1**, R = nC_4H_9) being only weakly active, and the *N,N*-dihexyl compound (**1**, R = C_6H_{13}) inactive (Szára, 1961a). None of these compounds, with the exception of *N,N*-dimethyltryptamine already referred to, appear to be found in nature.

Tryptamines with substituents in the benzene ring of the indole



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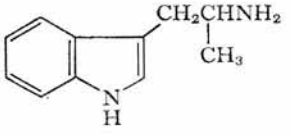
nucleus also possess psychotomimetic activity. One of the best known of these is *N,N*-dimethyl-5-hydroxytryptamine (**2**, R = CH_3, R′ = 5OH; bufotenine).

Bufotenine was first isolated from the secretions of the toad *Bufo vulgaris* by Bertrand and Phisalix in 1893 but its structure was not identified for another 41 years (Wieland *et al.*, 1934). It is, like *N,N*-dimethyltryptamine, present in cohoba snuff and was assumed by Fish *et al.* (1955) to be its main active constituent. This appears not to be the case, however, since intravenous doses of 2–16 mg/kg have been reported as producing psychotomimetic effects in man (Fabing and Hawkins, 1956) and, as was pointed out by Turner and Merlis (1959), it is unlikely that sufficient amounts of the drug would be absorbed by inhaling snuff. The latter authors, and subsequently others, have in fact questioned the psychotogenicity of bufotenine.

There is no question that *N,N*-dimethyl-4-hydroxytryptamine (**2**, R = CH_3, R′ = 4-OH; psilocin) and its derivative 3-2′-dimethylaminoethylindol-4-yl phosphate (**2**, R = CH_3, R′ = 4-OPO_2OH; psilocybin), are psychotomimetically active. These substances were isolated from a mushroom, *Psilocybe mexicana* (Agaricaceae), by Hofmann *et al.* in 1958. Various fungi, mostly belonging to the species *Psilocybe*, were known as "magic" or "sacred" mushrooms and were used for many centuries under the name teonanácatl by Mexican Indians in religious ceremonies. It was not until 1956 that the fungi were identified by the French mycologist Heim.

Psilocybin and psilocin were soon tested in man. Oral doses of between 4 and 8 mg produced a syndrome very similar to that elicited by LSD-25 or mescaline (Hofmann *et al.*, 1959). Subsequent studies (Hollister, 1961; Wolbach *et al.*, 1962) have confirmed both the dose level and the similarities to LSD-25 and mescaline.

There is some dispute in the literature concerning the psychotomimetic activity of 6-hydroxylated *N,N*-dialkyl tryptamines. These were claimed by Szára (1961b) to be present in the urine of subjects who had been given *N,N*-dialkyltryptamines and Szára and Hearst (1962) reported that *N,N*-diethyl-6-hydroxytryptamine (**2**, R = C_2H_5, R′ = 6-OH) was about six times as potent as a psychotomimetic drug than its non-hydroxylated analogue. This claim was not substantiated by



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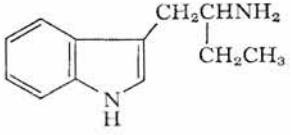

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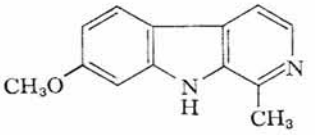
Rosenberg *et al.* (1963) who found no effect when intramuscular doses of 1 mg/kg were administered to human volunteers.

Tryptamines with branched side-chains are also psychoactive. α-Methyltryptamine (**3**) was shown by Murphree *et al.* (1960) to produce an LSD-25-like syndrome in man at a dose of about 20 mg. α-Ethyltryptamine (**4**) appears to produce different effects and was for a time on the market as an antidepressant drug.

2.1.2 *β-Carbolines*

The β-carbolines include harmine (**5**), harmaline (**6**), 1,2,3,4-tetrahydroharmine (**7**) and related compounds found naturally in a variety of plants, including the liana *Banisteria caapi* (Malpighiaceae), from which a beverage known variously as ayahuasca, yagé, pinde, huanto or caapi was prepared by South American Indians. Harmine is also found in the seeds of the Asian shrub *Peganum harmala* (Rutaceae), together with harmaline and its O-demethylated derivative harmalol.



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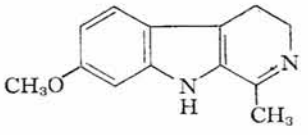

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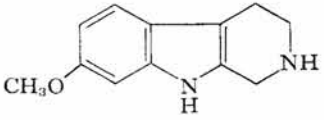
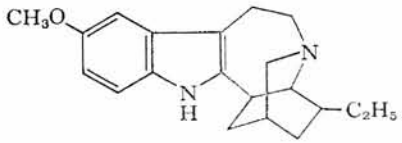


(**7**)

There is some dispute in the literature on the psychotomimetic activity of harmine. In an early report Lewin (1928) stated that subcutaneous doses of 25–75 mg caused euphoria in man. Later Pennes and Hoch (1957) reported LSD-25-like symptoms in mental patients given 300–400 mg of the drug intravenously but larger doses given orally had minimal effects. Turner *et al.* (1955) considered that the drug had no psychotomimetic activity. Crude extracts of *Banisteria caapi* are certainly active and it seems probable that the other constituents, harmaline and 1,2,3,4-tetrahydroharmine, are responsible, at any rate in part, for this activity. Such a view is supported by the finding of Naranjo (1967) that harmaline is psychotomimetic in man at intravenous doses of 1 mg/kg and oral doses of 4 mg/kg.

2.1.3 *Iboga alkaloids*

At least twelve alkaloids have been isolated from the root bark of the African shrub, *Tabernanthe iboga* (Apocynaceae). The root of the plant is chewed by certain natives of West Africa in order to combat tiredness, fatigue, and hunger (Tyler, 1966). If the amount consumed is large then inebriation, confusion, and hallucinations result (Landrin, 1905). The main alkaloid present in the root bark is ibogaine (**8**) but there is still some uncertainty concerning its psychotomimetic activity.



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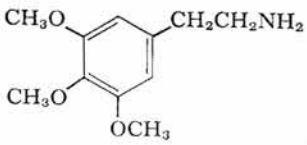
Animal experiments have shown that the drug produces central effects including fear and escape responses (Schneider and Sigg, 1957) and excitation and tremor (Zetler and Unna, 1959) but there do not appear to have been any studies in which the pure substance has been administered to man. Indeed Turner *et al.* (1955) expressed doubts as to whether ibogaine is a psychotomimetic substance.

2.2 PHENYLALKYLAMINES

Phenylethylamines occur commonly in nature, the best-known naturally occurring psychotomimetic drug of this type being mescaline. More recently some psychotomimetic phenylisopropylamines, synthetic analogues of amphetamine, have evoked a great deal of interest. Again, following the classification of Brown (1971), these two classes of drug will be considered in turn.

2.2.1 *Phenethylamines*

3,4,5-Trimethoxyphenethylamine (**9**, mescaline) occurs in various species of cacti, notably the dumpling cactus, *Lophophora williamsii*



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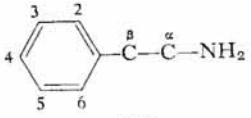
(Cactaceae), which grow in Central America. The sliced and dried heads of these cacti, known as mescal or peyotl, have long been used in their rituals by natives of these regions. The cactus was identified by Lewin in 1888; Heffter in a series of papers (1894, 1896, 1898, 1901) described the isolation and proof of the behaviour-modifying action of mescaline from this source. In 1919 Späth established the formula for mescaline.

Mescaline is not particularly potent as a psychotomimetic drug. The usual human oral dose is between 0.3 and 0.6 g (i.e. approximately 4–8 mg/kg). Initial autonomic effects are soon replaced by psychotomimetic effects which include hallucinations, disorientation in time and space, and depersonalization. The usual duration of effect is from 5 to 12 hours although there have been reports of prolonged effects persisting for 11 days in one case (Stevenson and Richards, 1960). There are many accounts of the signs and symptoms of mescaline intoxication. Early reports were summarized by Reti (1953). More recent accounts include those by Mayer-Gross (1951), Aldous Huxley (1954, 1956) and Deniker (1957).

Not unexpectedly many other phenethylamines, analogues of mescaline, have been studied. For example De Jong (1945) examined a series of such compounds for their "catatonizing power" and "fear-producing power" in experimental animals. The relevance of these effects to the psychotomimetic activity of the compounds is open to question but the results showed the importance of substitution in position 4 of the ring (**10**) for activity and also indicated that substitution on the α-carbon atom of the side-chain increased activity. The fear response was most marked with compounds bearing ethoxy substituents in the 4 position.



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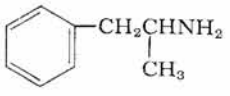
Another study was by Smythies and Levy (1960) in which the test used was a conditioned avoidance response in rats. The main conclusions were that the loss of the methoxy group in the 5-position of mescaline gave an approximate 50 per cent loss of activity and that replacement of the 4-methoxy group by a hydroxyl group eliminated activity whereas replacement by a benzyloxy group increased activity. The compound 3,4-dimethoxyphenylethylamine, reported by Smythies and Levy (1960) to possess about half the activity of mescaline, received considerable attention in the early 1960's when as "pink-spot" it was claimed (Friedhoff and Van Winkel, 1962) to be present in the urine of schizophrenic,

but not of non-schizophrenic subjects. This claim has since been refuted (Perry *et al.*, 1966) and studies on human volunteers have not shown any psychotomimetic activity of the compound (Shulgin *et al.*, 1966).

2.2.2 *Phenylisopropylamines*

Among the phenylalkylamines the most potent psychotomimetic drugs are phenylisopropylamines or amphetamine derivatives. Amphetamine (2-aminopropylbenzene) (**11**) does not conform to the definition of a psychotomimetic drug given at the beginning of this article, although it is clear that chronic users of the drug can develop a serious psychotic illness difficult to distinguish from schizophrenia.

An early report by Peretz *et al.* (1955) that 3,4,5-trimethoxyphenylisopropylamine (**12**, TMA) was twice as active as mescaline as a psychotomimetic drug in man has been followed by a series of studies, mainly by



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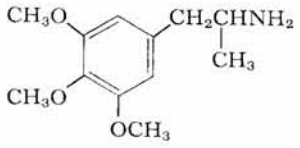
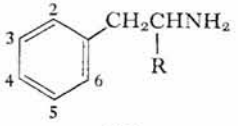


(12)

Shulgin and his colleagues, of the psychotomimetic activities of a large number of phenethylamines. This work was summarized by Shulgin *et al.* (1969) and by Shulgin (1970) and the structure–activity relationships will not be discussed in detail here but a few of the salient points will be mentioned.



(13)

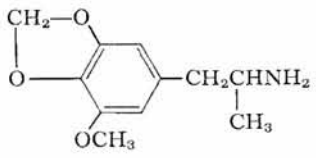
All the compounds studied conformed to the general structure (**13**). Considering the length of the side chain, activity was usually higher with a 3-carbon atom chain (**13**, R = CH_3) than with a 2- (**13**, R = H) or 4- (**13**, R = C_2H_5) carbon atom chain.

Introduction of a methoxy substituent into the benzene ring in position 2 almost always resulted in increased activity, whereas 3-methoxy substitution had the reverse effect. Substitution in the 4-position also tended to increase activity. The most active compound studied was 2,5-dimethoxy-4-methylphenylisopropylamine (STP, or DOM) (**13**, R = CH_3, 2,5-OCH_3, 4-CH_3), which was stated to be eighty times as potent as

mescaline as a psychotomimetic drug in man. Subsequently Faillace *et al.* (1970) reported that this drug in oral doses of between 2.7 and 3.3 mg produced symptoms similar to those resulting from LSD-25. This represents an activity about one hundred times greater than that of mescaline and agrees well with studies by other workers.

The close analogue of STP, 2,5-dimethoxy-4-ethylphenylisopropylamine, DOET (**13**, R = CH_3, 2,5-OCH_3, 5-C_2H_5), is apparently not psychotomimetic (Snyder *et al.*, 1970) but produces mild euphoria and enhanced self-awareness.

Another interesting compound in Shulgin's series is 2,5-dimethoxy-3,4-methylenedioxyphenylisopropylamine (**14**) synthesized because of its structural resemblance to myristicin (**15**) which is one of the main constituents of nutmeg, *Myristica fragans* (Myristicaceae), and possibly responsible for the psychotomimetic effects of large doses of nutmeg. This amphetamine derivative was about twelve times as active as mescaline.



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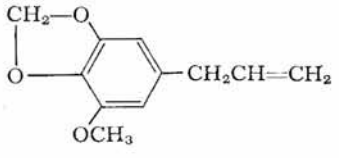
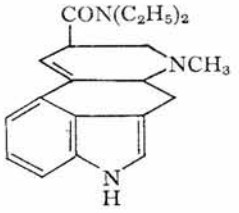


(**15**)

2.3 LYSERGIC ACID DERIVATIVES

The most potent psychotomimetic drug known is lysergic acid diethylamide (**16**, LSD-25), which was first prepared by Stoll and Hofmann in

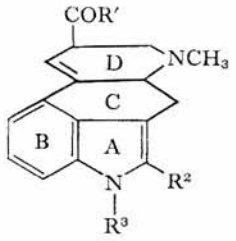


(**16**)

1938 from lysergic acid, but its profound psychotomimetic effects were not recognized until several years later (Hofmann, 1957). Various derivatives of lysergic acid are found in the fungus *Claviceps purpurea* (Hypocreaceae), the organism responsible for the ergot disease of rye. These derivatives are known as the ergot alkaloids and many of them are

pharmacologically active particularly in causing contractions of smooth muscle but none of the naturally occurring, semi-synthetic or synthetic derivatives so far reported are as active as LSD-25 as psychotomimetic drugs. The minimal effective dose of the latter in man, given orally or by intravenous or intramuscular injection, is about 0.5–1 μg/kg. There have been numerous accounts of its effects which include disturbances of sensation, particularly in the visual and proprioceptive systems, upsetting of thought processes and changes of mood. Hallucinations, particularly visual ones, are commonly reported as is depersonalization. There tends, however, to be a retention of insight.

Many other amides of lysergic acid have been synthesized and tested, mainly by workers at the Sandoz Laboratories in Basel (Stoll and Hofmann, 1955; Rothlin, 1957a, 1957b, 1957c). None of these are as



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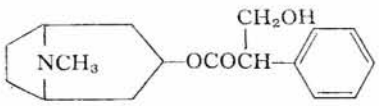
potent as LSD-25 as psychotomimetic drugs although it seems that the 1-acetyl derivative (**17**, $R^3 = COCH_3$) approaches it in activity. Activity is reduced but not completely lost when the diethylamino group of LSD-25 (at R^1 in **17**) is replaced by other amines. Saturation of the double bond in the D ring results in almost complete loss of activity as does substitution at R^2.

3 Antiacetylcholine drugs

Antiacetylcholine, or anticholinergic, or cholinolytic, or atropine-like drugs are defined pharmacologically by their property of acting as competitive antagonists to acetylcholine at its muscarinic, or post-ganglionic parasympathetic sites of action. That such drugs can have psychotomimetic activity has been recognized since it was realized that atropine (**19**), hyoscine (**20**) and related alkaloids are responsible for the toxic psychosis seen in cases of poisoning with *Atropa belladonna* and other Solanaceous plants.

There have also been reports of psychotic episodes following the



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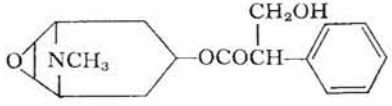

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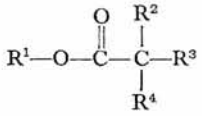
instillation of atropine eye-drops and the administration of sleeping preparations containing hyoscine (Hoffer and Osmond, 1967).

The most interesting psychotomimetic antiacetylcholine drugs are found among a serious of glycollic acid esters (**21**) first reported by



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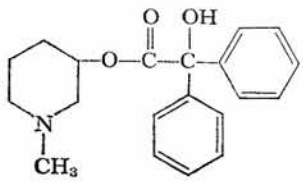
Abood *et al.* in 1958. Since then a number of these compounds have been synthesized and studied for their antiacetylcholine and psychotomimetic activity (Abood *et al.*, 1959; Biel *et al.*, 1961; Abood and Biel, 1962; Biel *et al.*, 1962; Biel, 1968; Abood, 1968). The structure–activity relationships (for psychotomimetic activity) among these drugs were summarized by Abood (1968). His main conclusions were as follows:

a. Where R^1 = N-substituted piperidine or pyrrolidine, the N-substituent must be a lower alkyl for maximal activity.
b. R^2 must be a hydroxyl group.
c. R^3 and R^4 can be the following combinations (in decreasing order of potency): cycloalkyl, phenyl; phenyl, phenyl; phenyl, unsaturated alkyl; cycloalkyl, unsaturated alkyl; phenyl, alkyl; cycloalkyl, alkyl; alkyl, alkyl.
d. Activity is lost following substitution by halides, alkyl, alkoxy, or phenyl in one or both phenyl rings of the acid moiety.
e. In the series where R^1 is N-substituted piperidine, greatest potency is found with the ester in the 4-position of the ring. Potency is reduced when it is in the 3-position and is smaller still when it is in the 2-position.
f. The thiol esters where -S- is substituted for -O- are less active and shorter acting.
g. Esters of 3-quinuclidinol compare in activity with the 4-piperidyl-4-cyclopentyl esters, whereas esters of 3-tropanol and 3-granatanol are somewhat less active.

Probably the three compounds in this series which have been studied most extensively are: 1-methyl-3-piperidyl benzilate (JB-336; **22**),



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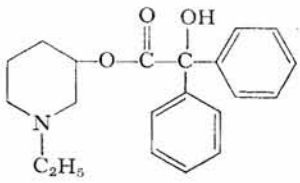

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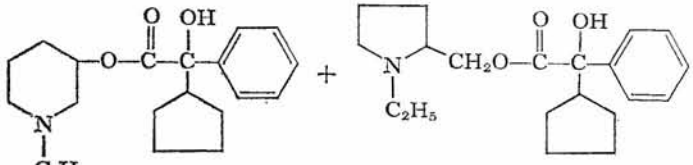


30% 70%

(24)

1-ethyl-3-piperidyl benzilate (JB-318; **23**), and Ditran (JB-329; **24**), a mixture of the benzilate esters of 1-ethyl-3-piperidinol and 1-ethyl-2-pyrrolidinylmethanol. These compounds are effective in producing psychotomimetic effects in man in oral, subcutaneous or intravenous doses of between 1 and 25 mg, i.e. about 0.02–0.35 mg/kg (Gershon and Olariu, 1960; Abood, 1968). By comparison clinical studies with atropine indicate that doses of 30–50 mg are required to produce psychotomimetic effects. Hyoscine is more potent, being effective at 0.8–4 mg (Miller, 1956; White *et al.*,1956; Ostfeld and Araguette, 1962).

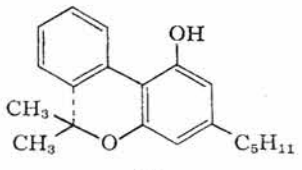
Hofmann (1968) has argued that the psychotomimetic properties of these drugs are due to toxic or side effects. However, others would claim (Gershon and Olariu, 1960; Finkelstein, 1961; Abood, 1968) that Ditran, for example, produces effects very similar to those seen in schizophrenia. Thus, thought processes are disrupted; speech is incoherent; confusion, disorientation and amnesia are common. Hallucinations occur mostly in the visual system though other sensory systems may be involved. These effects appear within 20 to 30 minutes and may persist for one or more days.

4 Cannabis and cannabinoids

For many centuries preparations of the Indian hemp plant, *Cannabis sativa* (Cannabinaceae), have been used in various parts of the world for their euphoriant and psychotomimetic effects. These preparations have a multitude of names depending on the area of the world from which they originate but also on the part of the plant used. There are two basic types

of preparation, the exudate or resin from the flowering tops or leaves known as hashish in the Middle East and North Africa and as charas in the Far East, and the chopped leaves or stalks commonly called marihuana. Cannabis preparations are usually smoked although they are also effective by mouth in the form of a tea or when cooked with, or embedded in, food.

It is only in recent years that the active principles in cannabis preparations have been identified with reasonable certainty. Smith and Smith showed in 1847 that the psychotropic activity resided in a non-alkaloidal, alkali-insoluble, high-boiling fraction which became known as red oil. In 1899 Wood *et al.* isolated from this a substance which they called cannabinol and whose structure (**25**) was elucidated by Cahn (1930, 1931, 1932, 1933). Adams *et al.* (1940a, 1940b) isolated and crystallized cannabinol from the Cannabis plant; additionally they isolated a new substance, cannabidiol (**26**).



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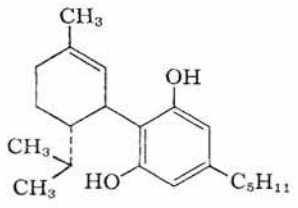
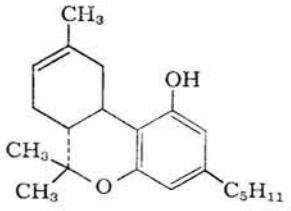


(26)

It soon became apparent, however, that neither of these substances possessed psychotomimetic activity and interest turned to the tetrahydrocannabinols (THC's). Adams *et al.* (1940c) showed that under acid conditions cyclization of cannabidiol occurs to form mixtures of optically active THC's. Biological activity resided in a high rotating compound shown to be Δ^8-THC (**27**) (Adams and Baker, 1940). This is a dibenzopyran existing, as do all the naturally occurring cannabinoids, in the *trans* conformation. Adams and Baker (1940) and Ghosh *et al.* (1940) also synthesized $\Delta^{6a,10a}$-THC (**28**) which was said to be about one-eighth as active as Δ^8-THC in man. This compound was much used between 1940 and 1965 as a standard for the biological testing of cannabinol derivatives. There has since been some dispute as to its psychotomimetic activity. Isbell *et al.* (1967) could detect no activity when it was administered to man by smoking but Hollister (1971) found it to be only 3 to 6 times less potent than Δ^9-THC (**29**, see below), when given by the same route. These doubts, together with the fact that mixtures of isomers, various plant extracts and synthetic compounds were used



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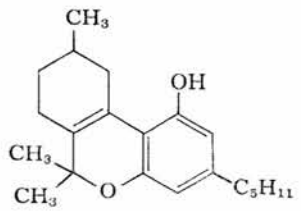

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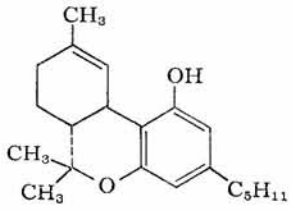
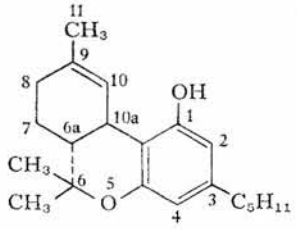


(29)

indiscriminately in biological studies, makes much of the work carried out prior to 1965 greatly open to question.

Another possible source of confusion arises from the use of different numbering systems for the THC's. Both formal pyran-type and monoterpenoid numbering systems have been, and still are, used. The result is that the same substance can be designated Δ^9-THC (formal pyran-type numbering, **30**) or Δ^1-THC (monoterpenoid numbering, **31**). The formal pyran-type numbering system is used here.



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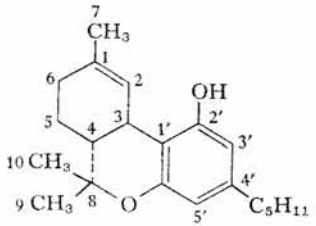


(31)

With the development of modern analytical techniques more compounds have been isolated from Cannabis extracts. Pioneers in this field were Mechoulam and his colleagues who, in the early 1960's, isolated nine compounds from red-oil. They considered Δ^9-THC (**29**) to be the major active principle (Mechoulam and Gaoni, 1965) although Δ^8-THC (**27**), present in smaller amounts, also possesses psychotomimetic activity (Mechoulam and Gaoni, 1967). More recently other compounds, known

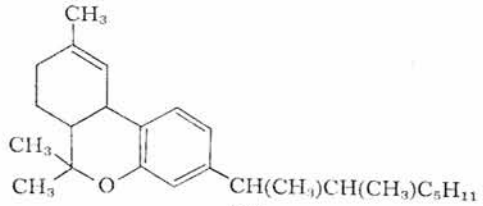
collectively as cannabinoids, have been isolated and Waller in 1971 listed sixteen of them. There is no strong evidence at present to suggest that any but Δ^8- and Δ^9-THC are biologically active. Their relative amounts vary with the preparation used (Taylor *et al.*, 1966; Lerner and Zeffert, 1968; Mechoulam *et al.*, 1970) although the Δ^9 isomer is almost always in the preponderance.

Synthetic methods are now available for both Δ^9- and Δ^8-THC. Petrzilka and Sikemeir (1967a, 1967b) and Petrzilka *et al.* (1969) described a stepwise synthesis of the THC's which was modified by Razdan *et al.* (1970) to give a single-stage synthesis of Δ^8-THC. This could then be converted through the chloro-compound to Δ^9-THC. Thus, pure materials are now available for biological studies although their lack of water solubility creates a problem.

Structure–activity relationships among cannabinoids have been studied, notably by Mechoulam and his colleagues (Mechoulam, 1970; Edery *et al.*, 1972). For details of their results reference should be made to the original papers but the main conclusions were as follows:

a. The tricyclic ring system is necessary for biological activity (measured in these experiments by a spectrum of effects on rhesus monkeys).
b. Substitution of a hydrogen on the aromatic ring of Δ^8- or Δ^9-THC with a carboxyl, a carbomethoxyl, an acetyl or an acetoxyl group abolishes or drastically reduces activity.
c. Alkyl substitution at C2 on the aromatic ring of the THC's (see **30**) gives a compound with reduced, but still appreciable, activity. Complete loss of activity results from substitution at C4.
d. Acetylation (at C1) of Δ^8- or Δ^9-THC gives active acetates.
e. The most active compounds studied were those in which modifications were made to the side chains of Δ^8- or Δ^9-THC. Three compounds, in particular (**32**, **33**, **34**), were more active than Δ^8-THC and at least equiactive with Δ^9-THC.

There have been several studies designed to determine the amount of the active principles Δ^8- and Δ^9-THC absorbed by cannabis smokers. One of the more thorough and more recent investigations, reported by Truitt (1971), led to the conclusion that of all the Δ^9-THC present in a cigarette about half is destroyed by pyrolysis, leaving the remaining half in the smoke or in the butt and so theoretically available for absorption. Similar results were quoted by Manno *et al.* (1970) but, in contrast, Claussen and Korte (1968) claimed that more than 90 per cent of the THC was destroyed by pyrolysis. Evidence is now accumulating for the biotransformation *in vivo* of Δ^8- and Δ^9-THC into active metabolites.



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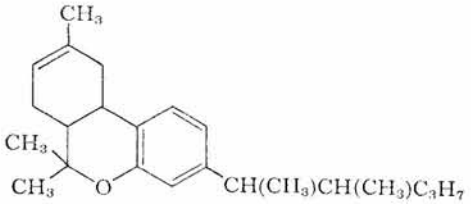

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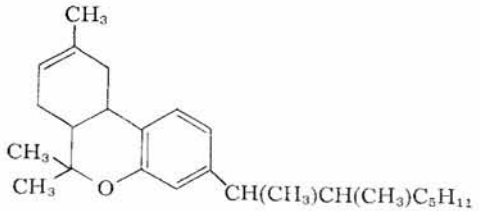
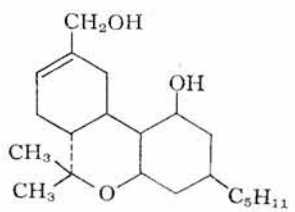


(34)

Burstein *et al.* (1972) injected tritiated Δ^8-THC into rabbits and, using mass spectometry, found 11-hydroxy-Δ^8-THC (**35**) in the urine.

Foltz *et al.* (1970) found 13 per cent of the injected radioactivity from ^{14}C-labelled Δ^8-THC in the livers of rats 30 minutes after injection, of this 65 per cent was the major metabolite which had the same R_F value as a metabolite formed *in vitro* when Δ^8-THC was incubated with a rat liver microsomal preparation and which was identified as 11-hydroxy-*trans*-Δ^8-THC (**35**).



(35)

Lemberger *et al.* (1971, 1972) showed in experiments with volunteers that 11-hydroxylation of THC also occurs in man after administration of the substance by intravenous injection or by smoking. The levels of 11-hydroxy-THC in the plasma seem to correspond well with the pattern of effects observed in Cannabis smokers. These effects are maximal within 15 minutes, are much less marked after half to one hour and are virtually absent after three hours (Weil *et al.*, 1968; Jones and Stone, 1970). All this provides strong evidence for 11-hydroxy-THC being responsible, at least in part, for the psychotomimetic activity of Cannabis. That the compound is active in man has now been demonstrated by Lemberger *et al.* (1972) and Perez-Reyes *et al.* (1972). The former workers gave tritiated 11-hydroxy-Δ^9-THC (1 mg; 24.6 μc) intravenously to volunteers. All experienced a psychological "high" which reached its peak between 2 to 3 minutes after drug administration. The latter group compared effects of Δ^9-THC and 11-hydroxy-Δ^9-THC given by intravenous infusion. The volunteers requested cessation of the infusion when they arrived at a desirable psychological state. The doses were 3.10 $\pm$ 0.09 mg of Δ^9-THC and 2.27 $\pm$ 0.81 mg of 11-hydroxy-Δ^9-THC, i.e. there was no significant difference between the doses. This appears to indicate that Δ^9-THC is active in its own right unless it is metabolized very rapidly indeed to its 11-hydroxy derivative.

It seems reasonable to assume on evidence currently available that the active principles of Cannabis are Δ^8- and Δ^9-THC and that the effects of the drug, described below, are due, at least in part, to 11-hydroxy derivatives of these compounds formed *in vivo*.

The main effects of Cannabis in man have been listed by Isbell (1971). Most consistently reported objective effects are tachycardia, conjunctival infection, and body sway. More subjective effects include elation, euphoria, sensory perceptual distortion, depersonalization, and hallucinations, although the latter only occur after large doses. The initial elation is often followed by sedation. The ability to think logically is impaired. The severity of the effects is related to dose and as far as can be determined it seems that the effects of crude preparations of Cannabis are proportional to their Δ^9-THC content. Similar effects occur after administration of the synthetic compounds $\Delta^{6a,10a}$-3-*n*-hexyl-THC (synhexyl, or pyrohexyl) or $\Delta^{6a,10a}$-3-*n*-pentyl-THC (**28**).

Since quantities of Δ^8- and Δ^9-THC became available for human experimentation a number of studies have been carried out to assess the effective doses of the compounds by different routes of administration. Isbell *et al.* (1967) compared the effects of 50 or 200 mg/kg Δ^9-THC in cigarettes with those of 120 or 480 mg/kg given by mouth. When increase in pulse rate was used as a measure of response it was found that the

compound was 2.6 times more potent when smoked than when taken by mouth. Allowing for the fact that, at the best estimate, only about half the material in a cigarette is available for absorption into the body, then the drug is probably five or six times more potent by smoking than by mouth.

Other studies (Isbell and Jasinski, 1969; Hollister and Gillespie, 1969; Jones and Stone, 1970; Melges *et al.*, 1970; Hollister, 1971; Kiplinger and Manno, 1971) indicate that the effective dose of Δ^9-THC by smoking lies between about 1 and 20 mg and by mouth between about 10 and 100 mg.

5 Biochemical and pharmacological actions

5.1 SYMPATHOMIMETIC AMINES

The majority of the pharmacological and biochemical work which has been carried out with this class of compound has been with LSD-25 and since most of the evidence which will be reviewed in this section relates specifically to that drug it is important to establish whether LSD-25 is typical of the class of compounds as a whole.

Superficially all indoleamines and phenylalkylamines appear to give rise to very similar mental effects, but, since it is very difficult to categorize and quantitate these effects, this does not constitute very powerful evidence for identical modes of action. More convincing is the fact that cross tolerance occurs between LSD-25 and various other compounds included in this class of sympathomimetic amines. Thus, for example, Hollister (1961) demonstrated cross tolerance between LSD-25 and psilocybin and Balestrieri (1957) and Wolbach *et al.* (1962) between LSD-25 and mescaline. More recently in my laboratory a cross tolerance has been shown in animal experiments between LSD-25 and the substituted amphetamine, STP. No cross tolerance could, however, be shown between LSD-25 and Δ^8-THC (Isbell and Jasinski, 1969) nor between LSD-25 and amphetamine (Rosenberg *et al*, 1963) or LSD-25 and the antiacetylcholine drugs hyoscine or *N*-ethyl-3-piperidyl benzilate (Isbell *et al.*, 1964). On this evidence, and taking into account the fact that, by definition, all the compounds possess a similar basic pharmacology as sympathomimetics, it seems reasonable to conclude, until contrary evidence is available, that they can be treated as a group with similar, if not identical, modes of action and that it is not unreasonable to assume that LSD-25 can be taken as a type compound. In this section some of the more important pieces of work with LSD-25 will be discussed and, where possible, reference will be made to similar work with other compounds in the class.

The first clue to a possible pharmacological basis for the psychotomimetic actions of LSD-25 arose from the work of Gaddum (1953). He showed that low concentrations of LSD-25 antagonized the actions of 5-hydroxytryptamine (5-HT; serotonin) on isolated gut or uterus. This led, fairly naturally, to the suggestion (Gaddum, 1954; Woolley and Shaw, 1954) that a similar antagonism at central 5-HT synapses might explain the psychotomimetic action of LSD-25.

The evidence for 5-HT having a role as a chemical transmitter on the central nervous system seems fairly powerful. It is certainly present in the brain (Twarog and Page, 1953; Amin *et al.*, 1954) where its concentrations vary with brain area, being highest in the hypothalamus and brain stem. Its localization in presynaptic nerve terminals has been demonstrated by studies employing differential centrifugation (Michaelson and Whittaker, 1962; Zieher and De Robertis, 1963) and fluorescence histochemistry (Hillarp *et al.*, 1966), and its microiontophoretic application to single brain neurones has resulted in changes in their rate of discharge (Curtis and Crawford, 1969).

However, the view that LSD-25 produces its psychotomimetic effects by a central antagonism of 5-HT received a setback when it was shown (Cerletti and Rothlin, 1950) that 2-brom-LSD (BOL-148; **16**, $R^1 = N(C_2H_5)_2$, $R^2 = Br$, $R^3 = H$), despite being a more potent antagonist of 5-HT peripherally than LSD-25, did not have psychotomimetic properties. Later it was shown by Roberts and Straughan (1967) that both LSD-25 and BOL-148 antagonized the effects of 5-HT applied iontophoretically to neurones in the cortex of the cat.

The whole question of this type of action of LSD-25 has recently been reopened by Boakes *et al.* (1970). They also used the technique of microiontophoresis and found that LSD-25 antagonized the 5-HT excitation of neurones in the brain stem of the cat. The methylated derivative of LSD-25, methysergide, which has also been reported as possessing psychotomimetic properties (Abramson and Rolo, 1967; Bender, 1970), also antagonized 5-HT excitation although it was not as potent as LSD-25. The non-psychotomimetic BOL-148 only rarely exhibited such antagonistic actions. Clearly, antagonism of 5-HT, specifically on neurones in the brain stem which are excited by this amine, must be considered as a possible mode of action of LSD-25 in producing its psychotomimetic effects.

Other workers have considered the possibility that LSD-25 exerts its effects by mimicking the actions of 5-HT. Certainly it has a similar excitatory action to 5-HT on isolated rat uterus (Costa, 1956) and on the clam heart (Welsh, 1957). In the latter test it has been claimed that relative potencies of analogues of LSD-25 correlated well with their

psychotomimetic potencies. Thus, although the precise manner and significance of the influences of LSD-25 on 5-HT synaptic functions are not understood, there is a distinct possibility that some kind of interaction between LSD-25 and 5-HT, and perhaps other brain amines, plays a role in its psychotomimetic action. This has led to a number of studies of the influences of LSD-25 and other psychotomimetic drugs on levels of amines in the brain.

One of the early studies was by Freedman and Giarman (1962) who found that doses of LSD-25 of 130 mg/kg to rats caused reproducible increases in brain 5-HT levels. The peak effect on brain 5-HT coincided with the termination of behavioural effects (disruption of food-motivated maze performance) (Freedman *et al*, 1964; Freedman and Coquet, 1965). Other psychotomimetic drugs, (+)-1-acetyl-LSD, psilocybin and mescaline produced very similar effects whereas the non-psychotomimetic agents, BOL-148, (+)-1-methyllysergic acid butanolamide, and methamphetamine did not (Freedman, 1963). Aghajanian and Freedman (1968) found very similar effects in rabbits, and many authors have now confirmed the findings with LSD-25, STP, (+)-1-methyl-LSD, mescaline, dimethyltryptamine, psilocybin and psilocin; most agree that with the rise in 5-HT there occurs a fall in levels of its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), suggesting that the rate of turnover of 5-HT is reduced (Diaz *et al.*, 1967; Freedman and Aghajanian, 1967; Rosecrans *et al.*, 1967; Andén *et al.*, 1968; Tonge and Leonard, 1969).

This suggested decrease in rate of turnover was demonstrated directly by Lin *et al.* (1969) who found that in rats LSD-25 decreased the conversion of ^{14}C-tryptophan into ^{14}C-5-HT. BOL-148, in higher doses, had no influence upon this rate of conversion. Opinions are not unanimous as to how this reduction in the rate of turnover is brought about. Freedman and his colleagues argued that diminished 5-HT turnover must imply some inhibition of 5-HT containing neurones, many of which are known to occur in the raphe nuclei of the medulla, pons, and lower mid-brain (Fuxe, 1965). Accordingly Aghajanian *et al.* (1968, 1970) and Foote *et al.* (1969) recorded the responses of raphe nuclei in the rat with systemically injected psychotomimetic drugs. They showed that LSD-25, mescaline, STP and *N,N*-dimethyltryptamine all inhibited firing rates of these neurones, while atropine, phencyclidine, hyoscine, and chlorpromazine did not. BOL-148 and methysergide were more than twenty times less active than LSD-25 in inhibiting firing. That the actions of the psychotomimetic drugs appears to be post-synaptic is indicated by the work of Couch (1970) who has shown that microiontophoretically applied 5-HT will excite raphe neurones while LSD-25

applied by the same method will block both 5-HT induced excitation of these neurones and the excitation produced by electrical stimulation of the brain stem reticular formation.

Andén *et al.* (1968) also assumed a post-synaptic site of action for LSD-25. They found that LSD-25 mimicked the effect of 5-HT on spinal reflexes and tremor and suggested that LSD-25 interacted centrally with 5-HT receptors. The decreased turnover of 5-HT they attributed to an inhibitory feedback mechanism operating on presynaptic 5-HT neurones. This view was shared by Tonge and Leonard (1969).

Other authors have suggested a more direct action of LSD-25 on presynaptic neurones. This suggestion is based to a large extent on resemblances between the actions of reserpine, which is known to act presynaptically, and those of LSD-25. Freedman and Giarman (1962) and Giarman and Freedman (1965) found that pretreatment with reserpine potentiated the elevation in brain 5-HT levels brought about by LSD-25. They also found that, like reserpine, LSD-25 had more effect on particulate than supernatant 5-HT. Attempts to elucidate these matters further in *in vitro* experiments have given results which are not easy to reconcile. Thus, Goodwin *et al.* (1969) found that LSD-25 inhibited the release of 5-HT from rat brain slices while Marchbanks *et al.* (1964) found that LSD-25 decreased 5-HT binding to the cellular fraction which is rich in synaptosomes.

The most likely conclusion is that the main action of LSD-25, and probably other psychotomimetic drugs in this class, is to interact with 5-HT receptors on the postsynaptic membrane. There also appears to be a presynaptic component in the action of the drugs, but whether this is indirect and operated via a feedback mechanism, or more direct, remains to be elucidated. The postsynaptic action probably results from a competition between 5-HT and LSD-25 for common receptors but whether these receptors are specifically for 5-HT or for tryptamines in general is not yet clear. Smythies *et al.* (1972) suggested that mescaline, *N*,*N*-dimethyltryptamine and LSD-25 all act on the 5-HT receptors in the brain. They backed up this suggestion by predicting from theory that certain new compounds would block the effects of these psychotomimetic drugs; in the particular rat behavioural situation used the predictions were confirmed. One difficulty with this hypothesis is to explain the very high potency of LSD-25 in comparison with other psychotomimetic drugs. Snyder and Richelson (1968) claimed that the bigger the psychotomimetic molecule the more potent was its effect. They explained this by suggesting that the molecule of LSD-25 fully fits the 5-HT receptor while smaller compounds fill it less completely. This explanation is not easy to accept without question when it is considered

that the presumed natural transmitter, i.e. 5-HT, which should fit the receptor perfectly, is a relatively small molecule.

The possibility that rather less specific tryptamine receptors are involved in LSD-25 action has been considered by Martin and Eades (1972). It had been shown earlier by Martin and Eades (1970) and Martin and Sloan (1970) that tryptamine has pharmacological properties in common with LSD-25 in the dog and in man; in their study in 1972 these authors were able to show a cross tolerance to tryptamine in dogs rendered tolerant to the effects of LSD-25. It is doubtful whether all workers would agree that tryptamine produces psychological effects in common with LSD-25; in fact it has been specifically stated (Sjoerdsma *et al.*, 1959) that the drug has no psychotomimetic properties. On evidence presently available, then, it is not possible to be precise about the nature of receptors with which LSD-25 and other psychotomimetics as well as 5-HT are presumed to interact.

The possibility that other brain amines are involved in the action of LSD-25 has also been considered but the picture is not so clear as it is with 5-HT. The most common finding (for example by Freedman, 1961) is that noradrenaline levels decrease concomitantly with the rises in 5-HT levels and it is tempting to conclude with Freedman and Aghajanian (1967) that shifts in the equilibrium of amines at central sites are of importance in the mode of action of LSD-25. Some of the most interesting work in this respect is by Leonard and Tonge (1968) and Tonge and Leonard (1969) who showed increases in levels of brain 5-HT in rats accompanied by decreases in levels of brain noradrenaline after administration of LSD-25 (200 μg/kg), mescaline (10 mg/kg), Ditran (4 mg/kg) and phencyclidine (10 mg/kg). The first two of these drugs are sympathomimetics. Ditran is an antiacetylcholine drug and phencyclidine a psychotomimetic anaesthetic which defies precise pharmacological classification. It is remarkable that drugs with such differing basic pharmacologies should produce such similar biochemical changes in the brain. The authors suggest, and this seems the most likely explanation, that the drugs may well act in different ways to produce the same net neurochemical changes. Whatever the precise nature of the biochemical changes brought about by LSD-25 and related drugs, these changes must be transduced into electrical phenomena before they can be reflected in changes in neurological functions and hence in behaviour. The effects of LSD-25 and other sympathomimetic psychotomimetics upon various aspects of the electrical activity of the brain have been much studied.

Many authors have shown that LSD-25 produces "alert" activity in the EEG, i.e. a pattern normally associated with alert behaviour and

characterized by high-frequency, low-amplitude waves. The same effect can be achieved by electrical stimulation of the brain stem reticular formation and it seems that the effects of both LSD-25 and amphetamine on electrocortical activity can be explained on the basis of a stimulation of the ascending reticular system (Bradley and Elkes, 1957), but there are differences between the actions of the two drugs in that amphetamine acts directly on the brain stem reticular formation while LSD-25 acts indirectly by facilitating input into the reticular formation via afferent collateral pathways (Bradley and Key, 1958). Subsequently Bradley and Marley (1965) studied the actions of tryptamine and some *N*- and α-alkyl tryptamines, some of which have been shown to be psychotomimetics in man. The actions of these drugs were complex. Initially they produced both behavioural and EEG arousal but soon the pattern of electrocortical activity changed to one of predominantly slow waves. This appeared to be due to a depressant action of the drugs on the brain stem reticular formation.

One of the most careful studies of the effects of sympathomimetic psychotomimetics on spontaneous electrical activity of the brain was by Fairchild *et al.* (1967) who compared the effects in the cat of amphetamine, mescaline and various ring-substituted amphetamines. The alterations in frequency distribution of spontaneous brain electrical activity were measured and two orthogonal patterns of frequency change were found which were correlated with dosage of the test compounds. The authors proposed that one of the patterns represented central alerting in the cat while the other was a correlate of the hallucinogenic or psychotomimetic effect produced in man by some of the drugs used. Amphetamine alone produced central alerting but the proven psychotomimetic 3,4,5-trimethoxyamphetamine, 3,4-methylenedioxyamphetamine and 3,4-methylenedioxy-5-methoxyamphetamine, were all more potent than mescaline in producing the "hallucinogenic effect" which was characterized by high-amplitude, low-frequency waves in the pattern of electrical activity recorded from both cortical and subcortical regions of the brain.

This brief and incomplete survey serves to show that there is no simple relationship between psychotomimetic activity of drugs and their effect upon spontaneous brain electrical activity. A provisional conclusion can be drawn that the high-frequency, low-amplitude pattern in the EEG which often follows administration of the drugs is merely a manifestation of their alerting activity and that the pattern of slow waves may be in some way correlated with psychotomimetic activity.

The apparent lack of a simple correlation between EEG effects and psychotomimetic activity is not surprising when it is realized that the recorded activity is contributed to by large, and presumably variable,

numbers of neurones. Results which seem easier to interpret have been obtained from studies on transmission in specific synaptic systems in the brain. Marrazzi and Hart (1955) found that electrical stimulation of the visual cortex of a lightly anaesthetized cat evoked a potential response at the corresponding point in the opposite cortex. An injection of 8 μg/kg LSD-25 into the carotid artery reduced the amplitude of the post-synaptic component of this transcallosal response. The specificity of this effect seems not to be very great for mescaline, 5-HT, adrenaline, noradrenaline, and adrenochrome: all had the same action (Elkes *et al.*, 1954), which may, therefore, be a consequence of the sympathomimetic actions of the drugs. Subsequent similar studies by Bond and Guth (1968) also indicated that doses of LSD-25 as low as 6 μg/kg depressed the evoked potential, and also that LSD-25 antagonized the depressant effect of 5-HT. The authors suggested that LSD-25 and 5-HT mutually displace each other from receptor sites which are involved in the depression of the transcallosal response.

There are many other reports of the effects of LSD-25 on evoked potentials in the auditory and visual systems. These are of obvious relevance in view of the actions of LSD-25 in producing auditory and visual hallucinations. Purpura (1956a, 1956b) used cats immobilized with succinylcholine and found that low doses of LSD-25 facilitated responses on the auditory cortex to click stimuli and on the visual cortex to photic stimuli. Higher doses (40–60 μg/kg), while still facilitating the visual response, depressed the auditory response. Purpura (1957) studied the effects of LSD-25 on the cortical potentials evoked by electrical stimulation of the lateral geniculate radiation fibres and of the homolateral suprasylvian gyrus (i.e. at different points along the visual pathway). From his results he concluded that the drug inhibited transmission across axodendritic synapses but facilitated transmission across axosomatic synapses.

Evarts *et al.* (1955) also studied the effects of LSD-25 on synaptic transmission in the visual system of the cat. They placed recording electrodes in the lateral geniculate body, in the geniculate radiation fibres, and in the retina. They found that geniculate transmission was blocked by doses of 30 μg/kg LSD-25 given by intracarotid injection but that transmission within the retina or between geniculate radiation fibres and cortical cells was extremely resistant to inhibition by LSD-25. Similar results were obtained with bufotenine. Curiously perhaps, the dose of LSD-25 required to block geniculate transmission in conscious animals was about five times higher than in animals anaesthetized with pentobarbitone.

Everts and his colleagues concluded that LSD-25 was acting as a

competitive antagonist at optic tract–lateral geniculate synapses. Bishop *et al.* (1959) supported this conclusion on the basis of their finding that a 10-minute optic tract tetanus overcame the LSD-25 block. Later when more refined techniques, notably microiontophoretic application of drugs to single neurones, became available, Curtis and Davis (1962) were able to confirm in the barbiturate-anaesthetized cat that LSD-25 antagonized lateral geniculate cell responses to optic tract stimulation. The apparent significance of this effect was, however, reduced somewhat by their finding that dopamine, noradrenaline, adrenaline, BOL-148, tryptamine, and 5-HT all produced similar antagonism. An assessment of the true significance of these findings must await the identification of the chemical transmitter at optic tract–lateral geniculate synapses. The best evidence currently available would seem to support the view that acetylcholine plays a transmitter role in the lateral geniculate with the effects of 5-HT being rather less specific.

These few examples will suffice to show that LSD-25 and related drugs are capable of modifying synaptic transmission in the brain. The form of the modification, that is whether there is facilitation or inhibition, seems to depend not only upon the dose of drug but also upon the neurones involved. In any case the result is likely to be a distortion in sensation and there is experimental evidence to support this view. Bradley and Elkes (1957), in the study referred to earlier, found that while amphetamine produced behavioural and electrocortical alerting irrespective of environmental conditions, i.e. by a direct action on the brain stem reticular formation, the degree of alerting produced by LSD-25 was related to the amount of stimulation from the environment, i.e. the drug affected sensory input into the reticular formation. The matter was taken further by Key and Bradley (1960) who used cats with chronically implanted cortical electrodes and conditioned the animals to respond to a sound stimulus by pairing the stimulus with an electric shock delivered to the feet. Once the conditioned response was established the animals responded to the sound stimulus 30 to 40 times without further reinforcements, i.e. without shock. The level of the stimulus gradually decreased during the process of conditioning and eventually reached a level which appeared to be close to the threshold of hearing for the cat. A dose of LSD-25 (5 μg intraperitoneally) did not affect the threshold of arousal to a stimulus of a pitch to which the animal had previously been conditioned, but the threshold for a stimulus to which the animal had not been conditioned fell sharply to a level approaching that to which the conditioned animal responded. Essentially these experiments indicated that LSD-25 treated animals became more sensitive to external stimuli, i.e. that LSD-25 increased the level of

significance of the stimuli. A similar finding was that of Key (1961) who reported that the rate of extinction of a conditioned avoidance response in cats was reduced if the animal was given LSD-25. This again suggests that the stimulus, in this case a tone, had increased significance for the animals. More recently Sheard and Aghajanian (1968) have attempted to elucidate the role of 5-HT in this effect of LSD-25 on rate of habituation. They electrically stimulated the caudal mid-brain raphe area (which has many 5-HT containing neurones) in rats. This resulted in a persistence of, or a lack of habituation to, the startle response to sudden sensory stimuli. No such hyperreactivity induced by raphe stimulation was seen in animals pretreated with *p*-chlorophenylalanine, a fairly specific depletor of brain 5-HT. The authors suggested that 5-HT is concerned in the persistence of the startle response and that LSD-25 mimics its actions in decreasing rate of habituation.

This brief summary of a very small proportion of the available evidence (for a more complete summary see Brawley and Duffield, 1972) allows some tentative conclusions to be drawn. It seems probable that LSD-25 and related drugs act as competitive antagonists to 5-HT at central synapses; other amines may also be involved. In neurophysiological terms the consequence of this action is modification of synaptic transmission, possibly facilitation at low doses and inhibition at higher doses. The consequent interference with normal sensory input almost certainly leads to misinterpretation of the sensory information and hence distortions in the senses.

The anatomical site of action of the drugs in the brain is by no means certain. Sensory pathways and the brain stem reticular formation have already been referred to but the effects of sympathomimetic psychotomimetics on affect, attention, and perception has led some authors to consider the limbic system as a possible site of action since that system is involved in just those functions. The brain areas concerned are the temporal lobe, the hippocampal formation, the amygdala, the hypothalamus, the cingulate gyrus, and connecting pathways. Immediate support for such a possibility comes from the work of Baldwin *et al.* (1957) who claimed that LSD-25 did not modify the behaviour of monkeys after temporal lobectomy. The remainder of the evidence rests largely on findings of modified electrical activity in these brain areas after administration of drugs. Schwarz *et al.* (1956) noted the appearance of 2–7 Hz rhythms in the electrogram recorded from the temporal lobes after both LSD-25 and mescaline. Passouant *et al.* (1956), using cats, found that LSD-25 caused long bursts of 3–4 Hz activity in the hypothalamus and septal areas. Approximately synchronous activity was recorded simultaneously from the cortex, but hippocampal rhythms were not

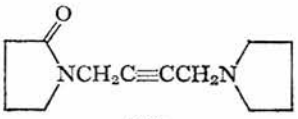
changed. On the other hand Adey *et al.* (1962) reported 4–5 Hz hippocampal "siezures".

5.2 ANTIACETYLCHOLINE DRUGS

By definition all antiacetylcholine drugs act as competitive antagonists of acetylcholine at post-ganglionic parasympathetic endings, the so-called muscarinic sites. The most obvious explanation for the psychotomimetic activity of these drugs is that they have a similar action in the central nervous system. For this explanation to be a possibility there must be a reasonable degree of certainty that acetylcholine functions as a chemical transmitter in the central nervous system, that it interacts with receptors which are analogous to peripheral muscarinic receptors, and that psychotomimetic antiacetylcholine drugs interfere with this interaction.

There can be little doubt that acetylcholine is a central transmitter. Bradley (1968) has summarized much of the evidence in favour of this view. Briefly, the case rests on the presence in the brain of acetylcholine and of the enzymes concerned in its synthesis and degradation and in the fact that the presence of cholinoceptive neurones in the central nervous system has been demonstrated using the technique of microiontophoretic application of drugs to single neurones. Studies of the latter type have also indicated that both muscarinic and nicotinic synapses are present in the central nervous system. Additional evidence for the presence of muscarinic receptors in the central nervous system was provided by the work of Bebbington and Brimblecombe (1965) and Brimblecombe (1970). This evidence can be summarized as follows:

a. Effects, notably tremors, produced by the muscarinic drug oxotremorine (**37**) are blocked by tertiary amine antiacetylcholine drugs but not by quaternary ammonium salts.
b. There is a good correlation between the peripheral muscarinic potencies of a series of acetylenic amines related to oxotremorine and their potencies in producing tremors.
c. The tremors are produced by tertiary amines, not by quaternary ammonium salts.



(37)

This evidence seems sufficient to justify an exploration of the possibility that antiacetylcholine drugs produce their psychotomimetic effects by antagonistic actions at central acetylcholine receptors. Investi-

gators have attempted to show correlations in series of drugs between their antiacetylcholine potency and their potency in producing either behavioural changes or changes in the electrical activity of the brain.

In 1959 Abood *et al.* claimed that there was no correlation between the psychotomimetic and antiacetylcholine activities of a series of piperidyl glycollates (**21**). Later Lipman (1967) made a similar claim but in both cases measurements of antiacetylcholine potency were made on peripheral tissues and are thus of little relevance to the central actions of the drugs. Other studies have contradicted this evidence. For example Herz (1963) showed a parallelism between the effects of a series of antiacetylcholine drugs on the electrical activity of the brain and on the behaviour of animals. He interpreted the results as indicating that a common antiacetylcholine mechanism was involved in the two actions. White and Carlton (1963) studied the effects of some piperidyl glycollates on the EEG of rabbits and concluded from their results that the drugs were acting via a central antiacetylcholine mechanism.

All centrally active antiacetylcholine drugs characteristically produce a phenomenon known as dissociation. Wikler (1952) first described this phenomenon in which animals are behaviourally alert while exhibiting EEG patterns normally associated with drowsiness or sleep. Brimblecombe and Green (1967, 1968) showed a statistically significant correlation between the potencies of a series of drugs in producing this dissociation in cats and their potencies in antagonizing oxotremorine-induced tremors in mice (assumed to be a measure of central antiacetylcholine potency). This constitutes evidence for the presence of cholinergic synapses in the mesodiencephalic activating system which is concerned with EEG arousal, but since the behavioural significance of the dissociation phenomenon is not clear this does not necessarily indicate that blocking actions of antiacetylcholine drugs at these synapses play any role in their psychotomimetic actions.

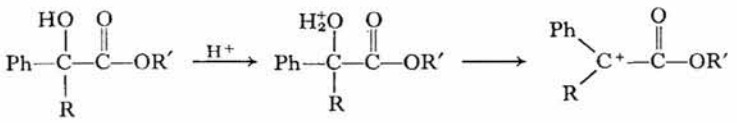
Attempts have also been made to correlate antiacetylcholine potencies of drugs with their potencies in modifying various aspects of animal behaviour. These studies also suffer from the drawback that the significance of any behavioural changes in terms of psychotomimetic activities in man are not clear. There is an additional complication in that all centrally-active antiacetylcholine drugs induce a state of hyperactivity in experimental animals, thus making the interpretation of the results of behavioural studies very difficult. This is perhaps the reason for the varied reported effects of antiacetylcholine drugs upon conditioned responses described by Longo in a review article written in 1966. The most common finding, however, is that the drugs disrupt the acquisition of conditioned responses, an effect which might perhaps be expected from

their reported amnesic properties in man. Brimblecombe and Buxton (1972) analysed the effects of a series of antiacetylcholine drugs upon avoidance conditioning of rats in a shuttle-box and on spontaneous activity in the same species. Although there was some indication that the drugs facilitated acquisition of the response this was shown to be, at any rate in part, an artifact due to the hyperactivity of the animals. The potency of drugs in producing this hyperactivity is correlated with their central antiacetylcholine potency (Inch and Brimblecombe, 1973). Thus, there is a good deal of suggestive evidence to support the view that antiacetylcholine drugs modify behaviour by central antagonism of acetylcholine. The answer to the question as to whether their psychotomimetic effects in man result from a similar action must await the accumulation of more human data. Such data as is available is not at variance with such a hypothesis. Reported psychotomimetic doses of hyoscine in man range from 0.8 to 4 mg and of atropine from 30 to 50 mg (Miller, 1956; White *et al.*, 1956; Ostfeld and Araguette, 1962), i.e. the ratio of potencies lies between about 8 and 60. The corresponding ratio for central antiacetylcholine potencies is about 13 (Brimblecombe and Green, 1968). In 1959 Abood *et al.* found that *N*-methyl-3-piperidyl benzilate was about twice as potent in man as its *N*-ethyl analogue. The ratio of central antiacetylcholine potencies of these two compounds is about 1.6:1.

It has already been intimated in this article that, at any rate in the view of the author, the most likely action of antiacetylcholine drugs in producing their psychotomimetic effects is a central antagonism of acetylcholine at muscarinic receptors. Nevertheless, certain biochemical actions of the drugs also warrant consideration as being possibly involved in producing the behavioural effects.

Abood and Rinaldi (1959) reported that tritium-labelled *N*-ethyl-3-piperidyl benzilate was localized in the central nervous system, mainly in a cytoplasmic granular fraction consisting largely of mitochondria, and it was concluded that the drug was bound to the mitochondria. Later, Abood and Biel (1962), recognizing the high phospholipid content of the mitochondria, suggested that the piperidyl glycollates interacted with the lipid portion of cell membranes. In experiments with frog sartorius muscle Abood and Biel obtained results which led to the conclusion that the drugs affected muscle depolarization by interfering with ionic movements, notably of Ca^{++} and Mg^{++}. The possibility of similar actions of the drugs on nerve cell membranes cannot be excluded.

Another suggestion by Abood (1968, 1970) was that a carbonium ion mechanism might be involved in the mode of action of the psychotomimetic glycollates, e.g.



The formation of a carbonium ion would destroy the asymmetry of the molecule and so stereochemical factors would not be expected to influence activity. Brimblecombe *et al.* (1971) showed that considerable differences in antiacetylcholine potencies exist between the enantiomers of compounds of this type. These authors also showed that pairs of enantiomers can have quite different durations of action. They would, however, be hydrolysed at the same rate, a fact which seems to invalidate Abood's suggestion that the duration of action of antiacetylcholine psychotomimetics is related to their ease of acid hydrolysis.

Perhaps the most interesting biochemical action of the antiacetylcholine drugs is that they cause decreases in the total acetylcholine content of the brain. This was shown, for example, by Giarman and Pepeu (1962) who suggested in 1964, as did Giarman and Freedman (1965), that the psychotomimetic activities of such drugs might be directly related to these changes in brain acetylcholine levels. It is very difficult to obtain direct evidence to confirm or refute this suggestion but it seems quite likely that the decreased levels are the consequence of cholinergic blockade, i.e. there is a feedback mechanism in operation. A possible hypothesis would be that antagonism at acetylcholine receptors is the primary action of the drugs leading to decreased acetylcholine synthesis and hence to decreased levels of the transmitter which may be responsible for the behavioural phenomena observed.

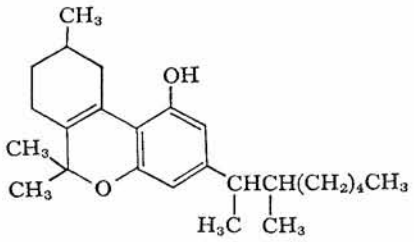
5.3 CANNABIS

There have been numerous studies of both peripheral and central pharmacological actions of Cannabis extracts and of pure cannabinoids both naturally occurring and synthetic. Clearly the central actions of the drugs are most relevant to their psychotomimetic activity and only brief mention will be made here of peripheral effects.

One study on isolated tissues by Gill and Paton (1970) was carried out to ascertain whether analogies with other drugs, suggested by the general pharmacology of Cannabis, could be detected. It was noted that the euphoria and some sympathomimetic effects were similar to those produced by cocaine, that euphoria and analgesia were reminiscent of morphine, the sensory disturbances similar to LSD-25, and the tachycardia to antiacetylcholine drugs. There also appeared to be a general

resemblance to the effects of alcohol and there were structural resemblances of Δ^9-THC with its phenolic hydroxyl group, to morphine and the catecholamines. The study was carried out on the guinea-pig vas deferens and the guinea-pig ileum, both excited by field stimulation. Various fractions of Tincture of Cannabis were used, one of which had an infrared spectrum identical to that of Δ^9-THC. The results indicated that three active principles were present. These were compared provisionally with atropine, with an alcohol, and with morphine or cocaine. These were purely operational comparisons, however, and should not be taken as indicating identical mechanisms of action with these drugs. The fraction which was almost certainly Δ^9-THC was the most potent and exerted effects at a concentration of 10^{-6} g/ml.

The cannabinoids have marked effects on the cardiovascular system (Hardman *et al.*, 1971). Synthetic THC derivatives with a double bond in the 6a,10a position produce marked hypotensive effects in dogs, cats, monkeys, and man. The most potent compound appears to be 1-hydroxy-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (**38**, dimethylheptylpyran, DMHP). The minimal effective dose to



(38)

produce hypotension in anaesthetized dogs was about 0.05 mg/kg. The effect appeared to be due mainly to a decreased sympathetic tone to peripheral blood vessels, but there was also some depression of medullary vasomotor sites.

Evidence relating to the naturally occurring Δ^9- and Δ^8-THC is conflicting. In squirrel monkeys Boyd *et al.* (1971) found that both compounds had marked hypotensive effects. In human studies Isbell *et al.* (1967) and Isbell and Jasinski (1969) reported no changes in blood pressure after intravenous administration of Δ^9-THC.

There are several reports of the analgesic activity of Δ^8- and Δ^9-THC. This is presumably a central effect (Bicher and Mechoulam, 1968; Buxbaum *et al.*, 1969; Buxbaum, 1972) but the results vary considerably with test method, species, solvent and route of administration (Harris, 1971). Thus, while it is clear that the drugs possess analgesic properties,

their profiles of activity differ from those of analgesics in clinical use. The synthetic compound DMHP (**38**) also has analgesic properties which are not reversed by the morphine antagonist nalorphine (Hardman *et al.*, 1971).

The production of hypothermia, also presumably central in origin, is a characteristic effect of cannabinoids. Hardman *et al.* (1957) showed that 1 mg/kg DMHP (**38**) given intravenously produced a reduction in the rectal temperature of dogs persisting for at least 24 hours. A similar long-lasting hypothermia in rats was produced by intraperitoneal doses of between 100 and 500 mg/kg Cannabis resin extract (equivalent to about 0.25–1.25 mg/kg THC) and by synthetic THC's (Miras, 1965). Garattini (1965) showed that intracerebral injection of a hashish extract to rats produced a hypothermic response thereby confirming the central origin of the effect. Holtzman *et al.* (1969) found that intraperitoneal doses of Δ^9-THC in excess of 1 mg/kg produced hypothermia in mice. It was claimed that the effect coincided with increased brain concentrations of noradrenaline and 5-hydroxytryptamine. The question of the effects of Cannabis on brain amines is discussed later in this section; the findings are by no means unanimous.

Hardman *et al.* (1971) drew attention to the similarities between the effects produced by reserpine and cannabinoids both of which produce hypotension and hypothermia. The biochemical action of reserpine is to deplete brain amines whereas cannabinoids seem, if anything, to elevate levels of some amines. It is difficult, therefore, to see any clear analogy between the modes of action of the two drugs.

Behaviourally, cannabinoids tend to produce signs of central nervous stimulation at low doses and of depression at higher doses (Bose *et al.*, 1964; Carlini and Kramer, 1965; Kubena and Barry, 1970). A typical study is that of Ferraro *et al.* (1971) in which it was shown that low doses of Δ^9-THC facilitated operant conditioning responses in chimpanzees while higher doses suppressed the responses.

A number of workers (Carlini, 1968; Silva *et al.*, 1968; Dewey *et al.*, 1969) have reported difficulties in obtaining dose-response relationships with cannabinoids in behavioural studies, especially when the drugs have been given repeatedly. This seems to be due to the development of tolerance as shown clearly by the experiments of McMillan *et al.* (1970a, 1970b). In these experiments the effects of a daily dose of 1.8 mg/kg Δ^9-THC on operant conditioning in pigeons disappeared within a week. Over the next three weeks the dose was increased to 36 mg/kg which in nontolerant birds would produce prostration. In some experiments pigeons have been brought gradually to 180 mg/kg which is above the lethal dose for non-tolerant birds. Cross-tolerance between Δ^9- and

Δ^8-THC and between Δ^9-THC and DMHP (**38**) and Δ^9-THC and Synhexyl (**36**) have been demonstrated in pigeons (Black *et al.*, 1970). The development of tolerance to DMHP has been demonstrated in dogs and monkeys by Hardman *et al.* (1971) but Lipparini *et al.* (1969), who gave 3 mg/kg Δ^9-THC intravenously to rabbits daily for six days, could find no attenuation of the behavioural responses to the drug nor to the effects on the EEG.

It appears that tolerance to the behavioural effects of Cannabis may not always be complete. Bueno and Carlini (1972) found that rats became tolerant to the effects of daily injections of a marihuana extract on rope-climbing behaviour but not to its effects on a lever-pressing task. Harris *et al.* (1972) found that monkeys given Δ^9-THC daily soon became tolerant to the effects of the drug on avoidance-responding but not to food-responding, both in a lever-pressing situation.

Other pharmacological actions of cannabinoids all emphasize their central nervous depressant actions. The hypothermic and analgesic effects already referred to are certainly due to such depression and potentiation of barbiturate sleeping time (Hardman *et al.*, 1971) is another characteristic effect of central nervous system depressants.

Similarly, the effects of the drugs on the electrical activity of the brain are what would be expected from depressant drugs. Domino *et al.* (1971) found that intravenous doses of 0.25 mg/kg DMHP given to dogs with chronically implanted brain electrodes caused the animals to become drowsy within about 20 min of the injections. Concurrently high-amplitude, low-frequency electrical activity was recorded from cortical and subcortical sites. Both the drowsiness and the electrophysiological effects could be reversed by various sensory stimuli or by 0.25 mg/kg (+)-amphetamine given intravenously. Similar effects of DMHP were seen in rhesus monkeys.

From these and other studies Domino *et al.* were able to draw some conclusions concerning the neuropharmacological effects of DMHP (and thus presumably of other cannabinoids). The main conclusions were:

a. There is a correlation between the pattern of electrical activity of the brain and the behavioural effects of the drugs.
b. The blockade of conditioned responses by cannabinoids is due mainly to confusional or depressant effects on higher centres of the brain rather than to depression of afferent input or impairment of motor output.
c. The primary site of action of the drugs appears to be in the cerebrum, especially in the secondary association areas and related subcortical structures.

d. DMHP has little effect on the mesodiencephalic activating system unless large doses are given when the arousal threshold is elevated.
e. Effects on the amygdala are primarily depressant.
f. Although slight depressant effects on the spinal cord can be detected they do not seem sufficient to account for the observed body swaying and depression of the flexor reflex.
g. Large doses of DMHP produce exaggerated startle responses sometimes including convulsive movements. The mechanism of this is unknown.

Boyd *et al.* (1971) considered that the distortions in sensory perception or in time sense experienced in man after cannabinoids and the hyper-reactivity to sensory stimuli observed in experimental animals could be due to effects of the drug on the non-primary or association areas of the cerebral cortex.

The overall picture, then, of the central pharmacology of Cannabis is one of a depressant drug, although low doses may be stimulant, the major site of action of which seems to be association areas of the cortex and related subcortical sites.

Most of the work aimed at elucidating the biochemical mode of action of Cannabis has been directed towards studying possible changes in concentrations of brain amines. The evidence is, however, conflicting and at this time no definite conclusions can be drawn. The reasons for this conflicting evidence are by no means clear. Undoubtedly some of them arise from the use of Cannabis extracts of doubtful and variable purity but even when pure Δ^9-THC or synthetic cannabinoids have been used results which are apparently completely contradictory have been obtained.

Some of the earliest experiments were those reported by Holtzman *et al.* (1969) who injected pure Δ^9-THC intraperitoneally to mice and measured levels of noradrenaline and 5-hydroxytryptamine (5-HT) in the brains at 45 minutes after injection. A spectrofluorometric method was used. It was found that doses of Δ^9-THC greater than 5 mg/kg increased the concentration of 5-HT in whole brains with significant increases being measured after 10, 100, 200, and 500 mg/kg. There were significant decreases in levels of noradrenaline after doses of 5 to 10 mg/kg but significant increases after 200 and 500 mg/kg. The time course of the changes in amine concentrations was followed and was found to correlate with the time course of the hypothermia in the animals. These effects were compared with those of other psychoactive drugs. It was noted that amphetamine and LSD-25 also lower brain noradrenaline and increase brain 5-HT but the behavioural response of the animals is

different in that they are hyper- rather than hypoactive. There was another difference in that no changes in levels of brain 5-hydroxyindoleacetic acid (5-HIAA) could be detected in animals which had been given Δ^9-THC, whereas levels of this metabolite of 5-HT were decreased after LSD-25 leading to the suggestion that LSD-25 decreases metabolism or increases binding of 5-HT (Rosecrans *et al.*, 1967).

Schildkraut and Efron (1971) used a dose of 80 mg/kg Δ^9-THC in rats and found only very small increases in brain 5-HT and small decreases in brain noradrenaline. Tritiated noradrenaline was administered intracisternally to these animals. Its rate of disappearance from the brain was accelerated and there was a small increase in its uptake in the brain. Unlike cocaine, amphetamine, monoamine oxidase inhibitors, and tricyclic antidepressants, Δ^9-THC did not appear to decrease the deamination of noradrenaline in the brain. The authors point out that it is not possible from their data to determine whether the reported effects on noradrenaline are due to specific actions of Δ^9-THC on central noradrenergic neurones or to an indirect action mediated through, for example, stress or hypothermia. The animals used in this study exhibited behavioural effects, notably hypoactivity and catalepsy although abnormal movements were also observed.

Pal and Ghosh (1972) studied the effects of doses of 10 or 100 mg/kg Δ^9-THC on the urinary excretion of 5-HIAA in rats. After repeated doses of 10 mg/kg or a single dose of 100 mg/kg significant increases were found in urinary 5-HIAA. The significance of this finding in terms of brain 5-HT metabolism is not clear since drugs may differentially affect 5-HT metabolism in different organs (Siva Sankar *et al.*, 1962).

Another study was by Ho *et al.* (1971) who studied the effects of Δ^9-THC given by inhalation from cigarettes to rats. Whole brain assays were carried out for noradrenaline, 5-HT and their metabolites, normetanephrine, and 5-HIAA. Repeated inhalation of Δ^9-THC did not affect levels of noradrenaline or 5-HT but resulted in decreased concentrations of both metabolites. The latter effect may have been due to an increased rate of transport of the metabolites from the brain.

A final example is the study by Gallager *et al.* (1972). They used lower, and they claimed more realistic, doses of THC in rats. The doses used (5.5 mg/kg intraperitoneally and 1 mg/kg intravenously) were sufficient to cause marked behavioural changes in the animals which were cataleptic, squealed characteristically, and displayed evidence of the antinociceptive effects of THC. No significant changes in levels of 5-HT or 5-HIAA in forebrain or brain-stem could be detected, neither was there any change in the rate of turnover of cerebral 5-HT.

These few examples will serve to indicate the confusion in the literature concerning the effects of cannabinoids on brain amine levels. It is tempting to conclude that these effects are seen only after large doses of the drugs and are, therefore, relatively non-specific. However, in a careful survey of the evidence, and partly as a result of experiments of their own, Truitt and Anderson (1971) reached the conclusion that Cannabis extracts and Δ^9-THC, in common with other psychotomimetic drugs (LSD-25, mescaline, and phencyclidine), caused significant increases in brain 5-HT levels while producing slight falls or no changes in levels of noradrenaline. They conclude, and there can be no argument with this conclusion, that "more complete studies of biogenic amine function will be required before the final mechanisms of THC on the brain are elucidated".

6 General Conclusions

It is abundantly clear that the three main classes of psychotomimetic drugs, the sympathomimetic amines, the antiacetylcholine drugs, and the cannabinoids, produce effects which, although appearing to be superficially similar, differ fairly considerably in detail. The mechanisms whereby they produce these effects are also almost certainly different. The sympathomimetic amines seem to compete with 5-HT for receptors, the antiacetylcholine drugs similarily compete with acetylcholine. Both these types of drugs give rise to central nervous system excitation, suggesting an inhibitory role for the chemical transmitters with which they compete. Cannabinoids, on the other hand, depress the central nervous system; their interactions, if any, with putative transmitter substances remain unclear.

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