Cannabis and the Brain
Recent Developments

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During the last 6 years there have been major advances in the understanding of the effects of cannabis-like ('cannabinoid') drugs on the brain. A specific cannabinoid receptor has been identified in the brain and has been cloned. More recently, a naturally occurring cannabinoid has been discovered in the brain. These advances have changed our understanding of cannabis as an illegal recreational drug, but have also exposed cannabinoid research as an area of fundamental significance for understanding the brain and behaviour. There is substantial evidence that cannabinoids impair cognitive processes, and these effects may be due in part to the action of cannabinoids in the hippocampus. However, some cannabinoids may also be useful therapeutically, particularly as analgesics. This review considers the implications of the latest developments in cannabinoid research for psychology and neuroscience.

Cannabis is one of the most popular recreational drugs in the world. In the U.S.A. alone it is estimated that in 1988 there were approximately 12 million cannabis users (Howlett, Bidaut-Russell, Devane, Melvin & Johnson, 1990a). In recent years there has been increasing debate as to whether cannabis use should be legalized in New Zealand. Part of this debate, which has taken place largely in the media, has focussed on the potential ill-effects of cannabis, particularly in the brain. However, the debate has ignored the striking advances in cannabis neuropharmacology which have occurred during the last 6 years. Principal among these advances has been the discovery of a receptor protein in the brain which is specific for cannabis-like ('cannabinoid') substances. Even more startling is the finding that there may be a naturally occurring cannabinoid in the brain (see Abbott, 1990; Howlett et al., 1990a, for reviews). These discoveries have not only changed our understanding of how cannabis affects the brain but have increased the probability that cannabinoids may be used to treat some neurological and psychiatric disorders.

The aim of this paper is to review recent advances in cannabinoid neuropharmacology and to evaluate their significance for psychology and neuroscience.

Cannabis - What Is It?

The term 'cannabis' is derived from the scientific name *(cannabis sativa)* for the marijuana plant, of which the major psychoactive component is Δ^9-tetrahydrocannabinol (Δ^9-THC) (Abood & Martin, 1992). The term 'cannabinoid' has been used to refer to any chemical which is structurally and/or functionally similar to Δ^9-THC, irrespective of whether it is naturally occurring or synthetic.

The introduction of this term was necessitated by the development of a large number of high-potency, synthetic analogues of Δ^9-THC, some of which are being tested as potential analgesics (see 'Therapeutic Potential' below) (Mechoulam, Devane, Breuer & Zahalka, 1991).

Behavioural Effects

The behavioural effects of cannabinoids are well-documented and have been reviewed extensively by Hollister (1986). The acute behavioural effects include sedation, weakness, fatigue, euphoria, rapid flow of thoughts, feelings of tranquility, dizziness, dry mouth, appetite stimulation and an impairment of perception

and memory. In addition, cannabinoids can induce analgesia, cause tachycardia (abnormally rapid heart beat) and reduce nausea and vomiting, bronchial constriction, intraocular pressure (in glaucoma) and seizure activity (Howlett et al., 1990a).

The chronic effects of cannabinoids are a matter of considerable controversy. While some researchers argue that chronic cannabinoid use can severely impair memory, others suggest that this happens only at very high doses. This issue will be discussed in detail in a later section on toxicity.

Evidence For A Specific Cannabinoid Receptor In The Central Nervous System (CNS)

The effects of cannabinoids on central nervous system (CNS) neurons have been reviewed previously (e.g, Martin, 1986; Dewey, 1986; Howlett et al., 1990a; Devane, 1994); however, most of these reviews were published before the discovery of the cannabinoid receptor.

Originally, it was thought that cannabinoids had non-specific effects on cells due to their capacity to dissolve readily through the lipid (ie., a constituent of fatty acids) component of the cell membrane (see Agurell et al., 1986 for a review). The first report of a specific cannabinoid receptor protein on CNS neurons was published by Nye, Seltzman, Pitt & Snyder in 1985. These authors found selective binding to neuronal membranes of the cannabinoid, [^{3}H]-5-'trimethylammonium Δ^8-THC. However, the distribution of these binding sites did not correlate well with those found in later studies, nor did the drug used by Nye et al. produce typical cannabinoid effects when administered to animals.

In 1988, Devane, Dysarz, Johnson, Melvin & Howlett used the synthetic cannabinoid analogue, CP-55,940, which is 10-100 times more potent than Δ^9-THC in vivo, in an attempt to label specific binding sites for cannabinoids. They found binding sites which were highly selective for CP-55,940. This first study used homogenate binding, in which large amounts of brain tissue were homogenized, labelled with the radioactive cannabinoid, and then the degree of radioactivity bound to the neuronal membranes was used as an index of the number of cannabinoid binding sites. Although this study identified specific binding sites, it was not possible to describe the spatial distribution of the binding sites in the brain. The latter objective required section autoradiography in which thin sections of tissue from different brain areas were exposed to the radioactive cannabinoid. In 1990, Herkenham et al. published the first description of the spatial distribution of cannabinoid binding sites in rat, rhesus monkey and human. In all 3 species, the highest densities of cannabinoid binding sites were in the neocortex, hippocampus, basal ganglia and cerebellum; lower densities were found in the brainstem and spinal cord (Herkenham et al., 1990).

More recent binding studies have confirmed the original findings (Bidaut-Russell, Devane & Howlett, 1990; Herkenham et al., 1991; Charalambous et al., 1991; Mailleux, Verslijpe & Vanderhaeghen, 1992a; Mailleux and Vanderhaeghen, 1992; Jansen, Haycock, Ward & Seybold, 1992; Thomas, Wei & Martin, 1992; Pacheco, Ward & Childers, 1993; Rodriguez De Fonseca, Gorrita, Fernandez-Ruiz, Paloma & Ramos, 1994a). Studies of the distribution of cannabinoid receptor messenger RNA have provided further confirmation (Mailleux, Parmentier & Vanderhaeghen, 1992b; Matsuda, Bonner & Lolait, 1993). The most recent studies suggest that there may be complex gender differences in the nature of CNS cannabinoid receptors (Rodriguez De Fonseca, Cebeira, Ramos, Martin & Fernandez-Ruiz, 1994b) and that cannabinoid receptors in the peripheral nervous system may modulate immune function (Munro, Thomas & Abu-Shaar, 1993; Lynn & Herkenham, 1994).

It is significant that many of the cannabinoid binding studies have used human tissue; as a consequence, there can be no question of the relevance of cannabinoid receptor research for the effects of cannabinoids in humans. In 1990, the rat cannabinoid receptor was cloned for the first time (Matsuda, Lolait, Brownstein, Young & Bonner, 1990). Since then, the human cannabinoid receptor has also been cloned and attempts have been made to model its 3dimensional structure (e.g, Thomas, Compton, Martin & Semus, 1991; Munro et al., 1993). Extensive investigations have been conducted to determine whether cannabinoid binding sites exist on a receptor complex for a known neurotransmitter or hormone. However, chemicals which mimick known neurotransmitters (e.g, noradrenaline, dopamine, serotonin, acetylcholine, opioids) or hormones (e.g, steroids) do not displace cannabinoids, suggesting that the cannabinoid binding site is independent of other receptors (BidautRussell et al., 1990). Nonetheless, there is evidence to suggest that cannabinoids may modulate non-cannabinoid receptors e.g, opioid receptors (Vaysse, Gardner & Zukin, 1987; Smith, Welch & Martin, 1994). Since opioid receptors have a multitude of functions, including the mediation of pain sensations, coughing, nausea, vomiting, the control of blood pressure and stomach secretions, and emotional responses, the indirect effects of cannabinoids on opioid receptors could have widespread behavioural consequences (see Julien, 1992 for a review).

The identification of specific binding sites on CNS neurons did not, in itself, prove that the cannabinoid binding site is part of a functional receptor. In order to prove that the cannabinoid binding site is functional, it had to be shown that the binding of a cannabinoid to the cannabinoid binding site affects neuronal function. At present, it seems that cannabinoids affect the concentration of a particular type of chemical messenger within neurons (ie., socalled 'second messengers') which brings about biochemical changes such as the activation of enzymes which modify the structure of protein. Cannabinoids have been shown to cause reversible inhibition of the production of the second messenger chemical, cyclic adenosine monophosphate (cAMP) (Bidaut-Russell et al., 1990). The binding of a cannabinoid to the extracellular cannabinoid receptor is believed to activate an inhibitory G protein, which inhibits the enzyme, adenylate cyclase, which normally converts adenosine triphosphate (ATP) to cAMP (Howlett, Qualy & Khachatrian, 1986; Bidaut-Russell et al., 1990; Howlett, Champion, Wilken & Mechoulam, 1990b; Audette, Burstein, Doyle, & Hunter, 1991; Pacheco, Ward & Childers, 1994).

Given the distribution of cannabinoid receptors in the CNS, it might be predicted that the most dramatic functional effects of cannabinoid administration would be in the neocortex, limbic system, basal ganglia and cerebellum. Metabolic studies, using the 2-deoxyglucose technique, support this prediction. Low doses (0.2 mg/kg) of Δ^9-THC increased glucose uptake in the limbic system and neocortex; however, high doses (2.0 or 10.0 mg/kg) reduced glucose uptake (Margulies & Hammer, 1991). Variable effects on glucose uptake have been reported in the cerebellum (Volkow et al., 1991).

Although a great deal of attention has been devoted to the actions of cannabinoids in the hippocampus and neocortex, it is clear that they also have important actions in other areas of the CNS. Cannabinoids have been shown to act directly on the hypothalamus, inhibiting the release of prolactin (which stimulates the development of mammary tissue during pregnancy and the postpartum production of milk), growth hormone (which regulates growth by increasing protein synthesis and blood glucose) (Tyrey, 1986; Rettori, Wenger, Snyder, Dalterio & McCann, 1988; Rodriguez De Fonseca et al., 1992a) and prostaglandins (some of which are involved in inflammatory responses) (Coupar &Taylor, 1982); they may also act directly on the pituitary gland, which mediates many of the body's hormone responses, including those related to physiological stressors (Murphy, Newton, Dhali & Chavez, 1991). Cannabinoids may induce changes in dopamine release in the basal ganglia (Navarro et al., 1993; Ng Cheong Ton et al., 1988), although this result has been questioned (Castaneda, Moss, Oddie & Whishaw, 1991). Despite the relatively low density of cannabinoid binding sites in the spinal cord, Δ^9-THC has been shown to have direct effects on spinal motoneurons (Turkanis & Karler, 1983).

Evidence For An Endogenous Cannabinoid

The discovery of a specific cannabinoid receptor naturally led to the question of why such a receptor should exist in the CNS. This in turn led to speculation that the nervous system might contain a naturally-occurring cannabinoid which, under some circumstances, would bind to the cannabinoid receptor.

The first report of an endogenous molecule which could interact selectively with the cannabinoid receptor was published in 1992 (Evans, Johnson & Howlett, 1992; Evans, Lake, Johnson & Howlett, 1994). In late 1992, Devane and colleagues isolated from the porcine brain an arachidonic acid derivative, arachidonylethanolamide, which could bind selectively to the cannabinoid receptor and produced similar effects to known cannabinoids. They called this naturally occurring cannabinoid, 'anandamide', following the Sanskrit word for'bliss' ('ananda'), and published its chemical structure (Devane et al., 1992). More recent studies have confirmed that anandamide has a similar range of pharmacological and behavioural actions to other natural and synthetic cannabinoids (Fride & Mechoulam, 1993; Crawley et al., 1993; Pertwee, Stevenson & Griffin, 1993; Kruszka & Gross, 1994; Childers, Sexton & Roy, 1994; Weidenfeld, Feldman & Mechoulam, 1994); mechanisms for the synthesis of anandamide have been suggested (Kruszka & Gross, 1994; Di Marzo et al., 1994) . At present, there is no clear answer to the question of what function(s) an endogenous cannabinoid might serve; however, the diversity of the behavioural effects of cannabinoids and the distribution of their binding sites suggests that the answer to this question will be complicated.

Evidence Relating to Toxicity in The CNS

Central to the cannabis debate has been the question of whether cannabis use results in impairment of psychological function (see Scarlet, 1991 for a review).

A number of human studies have suggested that cannabis use can result in impairments in cognitive function (e.g, Heishman, Huestis, Henningfield & Cone, 1990). In general, such studies demonstrate that chronic administration of marijuana can have adverse effects on cognitive processes, which last longer than the period of smoking (Heishman et al., 1990; Block, Farinpour & Braverman, 1992; Block & Ghoneim, 1993). However, it must be noted that the subjects in these experiments are usually experienced cannabis users who have volunteered for the study; therefore, there is an important element of self selection in the way that these

studies are designed (Heishman et al., 1990; Solowij, Michie & Fox, 1991; Block et al., 1992; Block & Ghoneim, 1993). The cognitive deficits (e.g, impairment of information retrieval, mathematical skills and verbal expression) are generally more severe in the case of 'heavy' chronic cannabis users than for occasional users (Block et al., 1992; Block & Ghoneim, 1993). Cognitive deficits have also been reported following acute administration of marijuana (e.g, Heishman et al., 1990; Block et al., 1992); however, since the subjects were marijuana users who were drug-free only for a short period before the experiment, the 'acute' effects were undoubtedly influenced by the subjects' drug histories. Event-related potential studies suggest that long-term cannabis use may result in attentional deficits which cause impairments in information processing (Solowij et al., 1991). Although many early studies were criticised because they used unrealistically high doses or abnormal routes of administration, more recent studies have attempted to use realistic drug administration protocols (Block et al., 1992; Block & Ghoneim, 1993). The results from animal studies are generally consistent with those on humans (e.g. Campbell, Foster, Hampson & Deadwyler, 1986a). In rhesus monkeys, at doses comparable to those used by humans when smoking marijuana, even a single, acute administration of a cannabinoid caused reduced responding on complex operant tasks e.g, delayed-matching-to-sample (Schulzs et al., 1988). However, some authors have suggested that reduced responding on discrimination tasks following cannabinoid administration is due to an impairment of motivation (e.g, Paule et al., 1992).

Given the contributions of the hippocampus to memory processes, a number of studies have examined the effects of cannabinoids on hippocampal electrophysiological activity, in particular the putative memory mechanism, long-term potentiation (LTP) (see Bliss & Collingridge, 1993 for a review). In the hippocampal slice maintained in vitro, low concentrations of Δ^9-THC have been shown to increase the duration of LTP, whereas high concentrations have been shown to reduce LTP duration (Nowicky & Teyler, 1987). In vivo studies have demonstrated that systemically administered Δ^9-THC suppresses sensory evoked discharges in the rat dentate gyrus and that these neuronal changes correlate with an impairment in discrimination behaviour (Campbell et al., 1986a; Campbell, Foster, Hampson & Deadwyler, 1986b). More recent studies suggest that Δ^9-THC may disrupt the processing of temporally specific information by the hippocampus, which may be the basis for the impairment of short-term memory by cannabinoids (Hampson, Foster & Deadwyler, 1989). Single neuron studies have demonstrated that, in delayed-matching-to-sample tasks, Δ^9-THC impairs the discharge of hippocampal neurons during the sample phase (Heyser, Hampson & Deadwyler, 1993).

Morphological studies of the long-term effects of Δ^9-THC have shown that it causes a decrease in neuronal density and an increase in glial cell reactivity in the hippocampus (Landfield, Cadwallader & Vinsant, 1988). Landfield and colleagues have suggested that some of the effects of cannabinoids may be via interactions with the corticosteroid systems (Eldridge & Landfield,1990). The corticosteroids (e.g, cortisol, corticosterone and aldosterone) have many complex functions, including the regulation of carbohydrate, protein and lipid metabolism, electrolyte and water balance, control of the cardiovascular system, the kidneys, skeletal muscle and neuronal function; given the widespread influences of corticosteroid systems, any drug which affects them could be expected to have equally widespread effects. Eldridge and Landfield (1990) have reported that cannabinoids compete with corticosteroids in binding to type II glucocorticoid receptors on rat hippocampal neurons. On the basis of these data, Eldridge and Landfield (1990) have advanced the hypothesis that cannabinoids, like corticosteroids, may cause aging-like degenerative changes in hippocampal neurons. Although it has been suggested that cannabinoids may inhibit the binding of acetylcholine (ACh) to muscarinic ACh binding sites in the CNS, recent studies have failed to confirm this result in vivo (Ali et al., 1991).

In addition to the evidence relating to memory impairment in adults, there is some evidence to suggest that maternal exposure to cannabinoids may alter neural function in the fetus. Fetal dopamine concentrations (Rodriguez De Fonseca, Hernandez, De Miguel, Fernandez-Ruiz & Ramos, 1992b), respiratory timing (Szeto, Wu, Cheng, Cheng & Decena, 1992) and EEG (Szeto, Wu, Decena & Cheng, 1991) have been found to change following maternal exposure to cannabinoids, although the changes may be short-lived (Szeto et al., 1991; Szeto et al., 1992). Nonetheless, young rats which are exposed to cannabinoids have been shown to exhibit behavioural deficits similar to those which occur following hippocampal lesions (see Scarlet, 1991 for a review); many reviewers conclude that cannabinoids pose a potential risk to the fetus (e.g. Nahas & Frick, 1986).

Therapeutic Potential Of Cannabinoids

Synthetic analogues of Δ^9-THC, e.g, nabilone, have been used as antiemetics for some time in the U.S.A. (see Howlett et al., 1990 for a review). However, one of the most exciting therapeutic possibilities for cannabinoids

is as analgesics. Some synthetic cannabinoids (e.g, levonantradol and desacetyllevonantradol) are reported to be 10-30 times more potent than morphine in analgesia tests in rodents (Reggio et al., 1991). Many patients with terminal diseases illegally smoke marijuana for its analgesic properties. At present, there are few data on the possible adverse effects or abuse potential of marijuana within such patient populations. However, attempts are being made to produce synthetic cannabinoids with high potency analgesic actions without other psychoactive effects (Reggio et al., 1991). One advantage of cannabinoid analgesics is that, compared to opioids such as morphine, they have fewer adverse side effects and a low risk of overdose (Howlett et al., 1990a). Therefore, cannabinoids may be comparatively safe analgesics.

Encouraged by the effects of cannabinoids in the basal ganglia, clinical trials have been conducted to determine whether cannabinoids may have therapeutic potential in the treatment of movement disorders such as Huntington's Disease. However, to date, most trials have indicated that cannabinoids have little, if any, therapeutic effect (e.g. Consroe et al., 1991). By contrast, some success has been reported with the use of dronabinol to stimulate appetite in cancer and HIV patients (Plasse et al., 1991). Despite the enthusiasm regarding the possible clinical potential of cannabinoids, it should be emphasised that endogenous cannabinoids and their receptors are a relatively recent discovery; it is therefore conceivable that the clinical use of cannabinoids could have unforseen adverse side effects. For example, recent studies demonstrate that cannabinoids can alter gene expression in the basal ganglia (Glass & Dragunow, 1995).

Conclusions

The last 6 years have seen major advances in the understanding of the effects of cannabinoids on the CNS and behaviour. Not only has a specific cannabinoid receptor been identified and cloned, but an endogenous cannabinoid has been discovered. These advances have not only changed our understanding of cannabis as an illegal recreational drug, they have exposed cannabinoid research as an area of fundamental significance for the understanding of CNS function and behaviour. It is too early to be certain of the role of cannabinoid receptors in normal CNS function or whether they are mainly involved in pathological processes. There is substantial evidence that cannabinoids impair various aspects of cognition, and increasing evidence that these effects may be at least partially mediated by the action of cannabinoids in the hippocampus. However, the potentially detrimental effects of cannabinoids should not cause us to lose sight of the therapeutic possibilities of these drugs. For example, there are circumstances (e.g. terminal illness) in which the chronic, adverse effects of cannabinoids may be less important than their efficacy as analgesics. In any case, continuing developments in cannabinoid pharmacology may eventually result in synthetic cannabinoids which have therapeutically useful effects with fewer adverse side effects.

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