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EDITORIAL

Medical uses of cannabinoids: the way forward

Most effects of Δ^9-tetrahydrocannabinol, the main psychotropic constituent of cannabis, are mediated by specific cannabinoid receptors, two types of which have so far been identified (Pertwee, 1997a). These are CB_1 receptors, cloned in 1990, and CB_2 receptors, cloned in 1993. Both these receptor types are coupled to their effector systems through $G_{i/o}$ proteins. CB_1 receptors are present in the central nervous system as well as in certain neuronal and non-neuronal peripheral tissues whereas CB_2 receptors are found mainly in cells of the immune system. Another important discovery has been that mammalian tissues produce cannabinoid receptor agonists, the most important being arachidonoylethanolamide (anandamide) and 2-arachidonoyl glycerol (Pertwee, 1997a). These endogenous cannabinoids and their receptors constitute the 'endogenous cannabinoid system'. As well as having physiological significance, the discovery of this system has important pharmacological and therapeutic implications. Indeed, drugs that selectively activate or block CB_1 or CB_2 receptors have already been developed (Pertwee, 1997a; Barth, 1998). Moreover, two cannabinoid receptor agonists, Δ^9-tetrahydrocannabinol and nabilone (a synthetic analogue of Δ^9-tetrahydrocannabinol), are licensed for use in the clinic to suppress nausea and vomiting provoked by anticancer drugs (USA and UK) or to boost appetite, particularly in AIDS patients (USA) (Pertwee, 1997b).

These recent scientific advances have been paralleled by growing pressure, not only from some scientists but also from patients who already self-medicate with cannabis, for greater clinical exploitation of cannabinoids and/or cannabis. Probably in response to this pressure, there have been a number of recent enquiries directed at collecting and evaluating current knowledge about the therapeutic potential of these drugs. For example, in November 1997 the British Medical Association published its report *Therapeutic Uses of Cannabis*, which calls for the setting-up of 'properly conducted clinical trials to evaluate the further potential therapeutic uses of cannabinoids'. Even more recently, the House of Lords Select Committee on Science and Technology established a Sub-Committee on Cannabis to look at the science behind the arguments over the use of cannabis and its derivatives for medical and recreational purposes. Its report was published in November 1998. This was followed in 1999 by the publication in the US of a report by the Institute of Medicine on the *Medical Use of Marijuana*. This may have been sparked in part by changes in the laws of California and Arizona (although not in Federal law) that have made it permissible to prescribe cannabis in these states as a medicine. Interestingly, whereas the ongoing 'Medical Marijuana' debate in the USA seems to be centred on the therapeutic potential of smoked cannabis, the debate in Britain is concerned more with new clinical uses of individual cannabinoids (and possibly also cannabis), administered to patients by routes that do not involve smoking.

Potential additional clinical uses of cannabinoid CB_1 receptor agonists include the suppression of some symptoms associated with multiple sclerosis (MS), with spinal injury and with certain other movement disorders (e.g. muscle spasticity/spasm), and with the management of glaucoma, bronchial asthma and pain. As detailed elsewhere (British Medical Association, 1997; Pertwee, 1997b), evidence supporting the use of CB_1 agonists for such purposes is based on anecdotal, preclinical and clinical data. The clinical data come from relatively few studies, often performed with very small numbers of patients. Even so, the consensus is that these findings are sufficiently promising to justify the setting-up of more extensive clinical trials that will test the medical efficacy of cannabis or indi-

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vidual cannabinoids conclusively. Further possible clinical uses for CB_1 receptor agonists emerge when one considers the basic pharmacology of these agents. There is evidence, for example, that CB_1 receptor agonists induce hypotension and bradycardia (Lake *et al.*, 1997) and that they inhibit intestinal motility (Calignano *et al.*, 1997; Pertwee, 1997a; Colombo *et al.*, 1998).

Cannabis and cannabinoids can also produce adverse effects. However, these seem to be no worse than those of accepted therapeutic agents (see Pertwee, 1997b). Some individuals may be more at risk from these unwanted effects than others (Hollister, 1986; Pertwee, 1997b). For example, cannabis may aggravate existing psychoses and can elevate heart rate. Consequently, it would be unwise to give psychotropic cannabinoids to patients with schizophrenia, coronary arteriosclerosis or congestive heart failure. The clinical significance of the ability of cannabinoids to retard fetal development, to induce fetal resorption in animals or to suppress immune function remains to be established. Because of the tars and gases produced during the combustion process, smoked cannabis is toxic to airway tissue and probably also carcinogenic (Hollister, 1986; British Medical Association, 1997; Roth *et al.*, 1998). However, cannabis is also active orally.

A number of difficulties stand in the way of further clinical cannabinoid research. One of these is that pharmaceutical companies are not showing particular interest in CB_1 receptor agonists, possibly because these drugs may only be effective at doses that are also psychotropic. Some companies are focusing on the search for possible clinical uses for CB_1 receptor antagonists (Barth, 1998). Agonists and antagonists for the CB_2 receptor have also attracted interest as potential medicines. However, as the physiological and pathophysiological roles of this receptor type remain to be established, it is fundamental rather than clinical research that is required in this area at present. In any case, it is the CB_1 receptor that seems to mediate effects such as relief from pain and spasticity. A way forward, then, may be to devise strategies that will separate the sought-after properties of CB_1 receptor agonists from their psychotropic effects. One possibility is to exploit known synergistic interactions between cannabinoids and opioids for antinociception (Pugh *et al.*, 1996) or between cannabinoids and benzodiazepines for inhibitory effects on motor function (Pertwee, 1992; Richter & Löscher, 1994). Whether such synergism would make it of therapeutic advantage to administer a cannabinoid in combination with an opioid or a benzodiazepine will depend largely on the extent to which the unwanted effects of these drugs are also augmented after combined administration. A second possibility is to develop drugs that activate the endogenous cannabinoid system indirectly by selectively inhibiting the metabolism or tissue uptake of endogenous cannabinoids so as to increase their levels at cannabinoid receptors (Pertwee, 1998). These drugs should be more selective than direct agonists as they are unlikely to affect all parts of the endogenous cannabinoid system at one time producing, instead, effects only at sites where on-going production of endogenous cannabinoids is taking place. Hence, just as monoamine levels can be enhanced to combat depression, so too modulation of endogenous cannabinoid concentrations at their sites of action could prove to be clinically beneficial. Another strategy for minimizing the unwanted central effects of cannabinoids may be to administer a high-affinity, low-efficacy CB_1 receptor agonist (affinity-driven agonist) such as 6′-cyanohex-2′-yne-Δ^8-tetrahydrocannabinol (O-823) (Pertwee *et al.*, 1996) rather than a high-efficacy agonist (efficacy-driven agonist). This is because it is to be expected that the ability of an agonist to elicit a response will be much more affected by variations in receptor concentration or coupling efficiency when the agonist is affinity-driven than when it is efficacy-driven. Since there are known to be significant regional variations within the brain, both in the concentration and in the coupling efficiency of cannabinoid receptors (Sim *et al.*, 1995; Pertwee, 1997a), it could well be that the effects produced by an affinity-driven cannabinoid receptor agonist *in vivo* are fewer in number and some of them also less intense than those produced by an efficacy-driven agonist. Consequently, an affinity-driven agonist for CB_1 receptors may possess fewer unwanted properties than an efficacy-driven agonist and yet still be capable of producing its sought-after effect(s). One disadvantage of such a drug is that its *in vivo* pharmacological effects are likely to be somewhat unpredictable. Finally, it may be possible to design cannabinoids that do not readily cross the blood–brain barrier but retain the abil-

ity to activate CB_1 receptors outside the brain so as to produce any sought-after effects mediated by peripheral CB_1 receptors.

A second difficulty is the dearth of outcome measures that will yield conclusive clinical data about drug efficacy, particularly for the relief of spasticity. Because of the psychotropic effects of CB_1 receptor agonists, there is also the problem of mounting trials that are truly blinded. In this case, one solution may be to include an active control, for example a benzodiazepine, and to work with patients who are not familiar with the effects of cannabis. For studies with cannabis, as opposed to Δ^9-tetrahydrocannabinol or nabilone there is the additional problem that cannabis is classified as Schedule 1, as this may limit experimental designs to those in which patients take the drug in the clinic under close supervision rather than at home.

When taken orally, Δ^9-tetrahydrocannabinol seems to undergo somewhat variable absorption from the gastrointestinal tract and to have a rather narrow 'therapeutic window' (see Pertwee, 1997b). This makes it difficult to predict an oral dose of a cannabinoid that will be both effective and tolerable to a patient. Consequently, there is a need for better cannabinoid formulations and modes of administration, possibilities including cannabinoid administration by rectal suppository, by skin patch, by direct application to the eye (for glaucoma) or by aerosol inhalation. Such absorption difficulties may account for anecdotal claims that cannabis is superior to Δ^9-tetrahydrocannabinol as a medicine as the comparison is usually between smoked cannabis (fast, reliable absorption) and oral Δ^9-tetrahydrocannabinol (slower, less reliable absorption). However, it is also possible that, in addition to Δ^9-tetrahydrocannabinol, there are other constituents of cannabis that contribute to its putative beneficial effects either directly or by modulating the effect(s) of Δ^9-tetrahydrocannabinol (Takahashi & Karniol, 1975; Dewey, 1986). There is an urgent need for a clinical study in which the efficacies and acute adverse effects of cannabis and an individual cannabinoid such as Δ^9-tetrahydrocannabinol are compared using the same route of administration.

In conclusion, there is sufficient evidence to warrant additional clinical studies with CB_1 receptor agonists. These should be directed at providing objective and conclusive answers to the following questions. First, do cannabinoids have efficacy against selected symptoms that is of clinical significance and, if so, do the benefits outweigh the known risks? Secondly, does cannabis have any therapeutic advantages over individual cannabinoids such as Δ^9-tetrahydrocannabinol? Thirdly, is there a significant need for additional drug treatments to manage any of the disorders against which cannabinoids may prove to be effective? An observation that children respond to the antiemetic effects of tetrahydrocannabinol without experiencing psychotropic side effects (Abrahamov, Abrahamov & Mechoulam, 1995) also merits further investigation. Additionally, it will be important to assess the clinical significance of the known ability of cannabinoids to induce signs of tolerance and dependence (Pertwee, 1991). To succeed, clinical studies with cannabinoids will require adequate funding and the committed involvement of scientists and physicians with appropriate cannabinoid and clinical expertise.

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