Editors' view

Exploiting modern cannabinoid
pharmacology for therapeutic gain?

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An excavation of the 2700-year-old Yanghai tombs near Turpan, Xinjiang-Uighur Autonomous Region in China, revealed the grave of a shaman whose accoutrements included a large cache of *Cannabis sativa* (the hemp plant), suggesting that cannabis was used as a pharmacological agent, whether with recreational, religious or therapeutic intent, in this pre-Silk Road culture [1]. Despite a long history of recreational use, however, cannabis has contributed relatively little to therapeutics, because of legal restrictions and because of its adverse effects. Nabiximols (USAN, trade name Sativex, synonym dronabinol/cannabidiol) is a cannabis extract formulated as an oromucosal spray and developed for symptoms such as neuropathic pain, spasticity and overactive bladder in patients with multiple sclerosis. Clinical trials to date have demonstrated modest and variable efficacy (<http://en.wikipedia.org/wiki/Nabiximols> accessed 11 March 2012). Nabilone is a synthetic cannabinoid licensed for use as an anti-emetic in patients with nausea and vomiting caused by cytotoxic chemotherapy and unresponsive to other anti-emetics. In contrast to the modest data supporting clinical utility, massive strides were made during the latter years of the twentieth century in the science of cannabis pharmacology. We hope that this will lead to new and more successful therapeutic applications and the purpose of this editors' view is to set this scene.

Δ^9 -tetrahydrocannabinol (THC, dronabinol) was identified as the main psychoactive component of cannabis in the 1960s (appropriately enough). It produces a mixture of depressant and psychotomimetic effects, including relaxation and a sense of well-being, coupled with sharpened sensory awareness – sights and sounds seem more intense and fantastic [2]. Measurable effects include impaired memory, learning and motor performance, hypothermia, analgesia, anti-emetic action and increased appetite. Various centrally mediated autonomic effects include tachycardia, vasodilatation (especially of the scleral and conjunctival vessels), reduced intraocular pressure and

bronchodilatation. Tolerance and some degree of physical dependence can occur in heavy cannabis users with abstinence symptoms being qualitatively similar to withdrawal from ethanol or opiates, but less intense.

Cannabinoid (CB) receptors

Specific cannabinoid receptors and their subtypes were identified in the 1980s and 1990s. CB₁ receptors are among the most abundant in brain tissue, being comparable in density with receptors for γ -aminobutyric acid (GABA), the main inhibitory central nervous system (CNS) neurotransmitter. They are concentrated in the hippocampus, cerebellum, hypothalamus and mesolimbic pathways – relevant to cannabinoid actions on, respectively, memory, coordination, appetite and temperature control and psychological reward. By contrast, CB₁ receptors are less extensively expressed in the brain stem and cannabinoids are less liable to cause respiratory and cardiovascular depression than opioids or ethanol. CB₁ receptors are located presynaptically and (like opioid receptors) are G-protein coupled. They inhibit adenylyl cyclase, inhibiting Ca²⁺ entry via voltage operated calcium channels and opening inwardly rectifying potassium channels that hyperpolarize the nerve terminal, thereby reducing neurotransmitter release. CB₂ receptors are present in the immune system (lymphoid tissues such as spleen, thymus and lymph nodes, as well as circulating lymphocytes and macrophages and microglia). Their function remains somewhat enigmatic, although they are expressed in atherosclerotic lesions and CB₂ agonists have anti-atherosclerotic effects [3].

Endocannabinoids

The discovery of specific CB receptors prompted the question whether there are endogenous ligands (analogous to

Figure 1

Cannabinoid (CB) pathways. Exogenous cannabinoids such as tetrahydrocannabinol (THC), or endogenous cannabinoids such as anandamide or 2-arachidonoyl glycerol (2-AG), produce their effects via G-protein coupled CB receptors. Endocannabinoids are synthesized from glycerophospholipid (GPL) by a phospholipase C (PLC) pathway to 2-AG or by a phospholipase D (PLD) pathway to anandamide. 2-AG is inactivated by monoacylglycerol lipase (MAGL) while anandamide is inactivated by fatty acid amide hydrolase-1 (FAAH1) which is irreversibly blocked by PF-04457845. 1-acyl-2AG, Sn-1-acyl-2-arachidonoyl glycerol; DAGL, diacylglycerol lipase; PE, phosphatidylethanolamine; NAPE, N-acyl phosphatidylethanolamine; NAT, N-acyltransferase

Hughes & Kosterlitz's earlier insight that led from the discovery of μ -opioid receptors to discovery of the enkephalins and then the endorphins [4]), and elegant combined ligand-binding and functional bioassay studies identified N-arachidonylethanolamide ('anandamide' – a Sanskrit derivation meaning 'bliss amide') from extracts of pig brain [5]. Several other putative endocannabinoids have subsequently been identified, most securely 2-arachidonoylglycerol (2-AG). The biosynthesis and breakdown of anandamide and 2-AG are summarized in Figure 1, from which it will be seen that their breakdown depends on different mechanisms. The relative contributions of anandamide and 2-AG in different physiological and pathological conditions are unknown, and drugs that selectively inhibit the breakdown of one or other could have distinct pharmacological effects and therapeutic uses.

Novel therapies?

CB agonists and antagonists are undergoing clinical trials for a wide range of potential indications including inflammatory bowel disease, fibromyalgia, neuropathic pain, alcoholism and other addictions and bipolar disorder (<http://www.clinicaltrials.gov> accessed 12 March 2012). Rimonabant, an inverse CB₁ agonist, caused substantial additional dose-related weight loss over 1 year vs. placebo in diet treated patients [6], but its marketing authorization

in Europe proved to be a false dawn. A committee advising the US FDA voted against approval because of concerns over suicidality, depression and other related adverse reactions. A drug that does the inverse of causing bliss must always have been an uncertain bet and, after further studies focusing on psychiatric symptoms, it was withdrawn.

Rather than administer an exogenous agonist, an alternative strategy is to potentiate endocannabinoid function. This strategy does not have too extensive a track record with other mediators (although cholinesterase inhibitors for myasthenia gravis and monoamine oxidase inhibitors, tricyclic antidepressants and selective serotonin re-uptake inhibitors for depression are possible 'role models'). However, hope springs eternal, and in this issue of the Journal we publish an elegant series of investigations of PF-04457845, an inhibitor of fatty acid amide hydrolase-1 (FAAH1), administered for the first time to humans [7]. Inhibition of this enzyme has been proposed as a way of mimicking the analgesic effects of exogenous cannabinoids without producing their undesired effects on cognitive function [8, 9]. Behavioural studies in mice that lack the gene for FAAH1 and in mice treated with FAAH1 inhibitors support the plausibility of this hypothesis.

In the present investigation a synthetic drug, PF-04457845, was administered to healthy volunteers in single and multiple rising dosage schedules, with a suitably conservative starting dose and maximum dose defined by animal toxicokinetic data [7, 10, 11]. Pharmacology

kinetics (PK) following low single doses suggest target-mediated drug disposition¹, but at higher doses and during repeated once daily administration for 14 days this mechanism is saturated and the PK parameters, $C_{\max}$ and AUC, appeared linear over the dose range studied (notably estimates of $t_{1/2}$ on day 14 in the multiple dose study varied only from 18.5 h in the 0.5 mg once daily regimen to 21.9 h in the 8 mg once daily regimen). Pharmacodynamic (PD) endpoints were FAAH1 activity measured in peripheral white blood cells and concentrations in plasma of anandamide and of other fatty acid amides (N-palmitoyl-, N-oleoyl- and N-linoleoyl-) that are substrates for FAAH1 and endocannabinoid candidates [8]. Once daily dosing readily achieved >97% inhibition of white blood cell FAAH1 activity and marked (3.5–10 fold) and prolonged (up to 2 weeks after stopping dosing) increases in plasma fatty acid amide concentrations, with an adverse reaction profile similar to placebo. There were no detectable effects on a range of cognitive function tests, including spatial memory, problem solving, psychomotor function, attention and memory. Peripheral biomarkers may not accurately reflect what is happening in the central nervous system, and the million dollar question is, of course, what effects (if any) will PF-04457845 exert in chronic painful disease and/or in pain models [12] or in the other potential therapeutic targets mentioned above. We await the outcome of such studies with bated breath, since if positive the new approach inaugurated by the translational investigations of Gai Ling Li and colleagues could be a game changer!

Competing Interests

There are no competing interests to declare.

¹Ascending single oral doses of PF-04457845 caused supraproportional drug exposure typical of target-mediated drug disposition, often observed with macromolecular biologicals and less often with small molecular weight drugs. See [7] for a fuller explanation and for references.

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