in OCT, endoscopes and fiber-optic catheters could overcome the problem that the penetration depth of the technique is limited to a few mm. OCI could also be of use to scientists involved in drug development. For example, investigators could monitor how a drug penetrates superficial tissue or whether a drug changes diseased tissue.

Gregory Farber at the National Center for Research Resources (Bethesda, MD, USA), which is funding the research, says 'It is probably fair to say that we have not yet worked out all the possible applications. The important thing is that it offers yet another imaging technique.' Turek agrees: 'Because of the nature of how the information is collected, OCI has the potential to give us information from biological tissues that we might not be able to get with other methods.'

Reference

1 Yu, P. *et al*. (2002) Visual fly-throughs of rat osteogenic sarcoma by optical coherence imaging. *Conference on Lasers and Electro-Optics* (CLEO 2002), 19–24 May 2002, Long Beach, CA, USA, Paper no. CthI4

New cannabinoid for multiple sclerosis

Jo Whelan, freelance writer

A new synthetic cannabinoid could provide symptomatic relief from muscle spasticity and tremor in people with multiple sclerosis (MS), without psychoactive side effects. Ajulemic acid (CT-3) has already completed Phase I clinical trials to determine its safety and tolerability, and has recently demonstrated anti-spastic activity in a mouse model of MS.

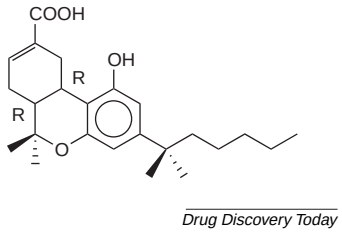
MS and cannabis

Multiple sclerosis is an autoimmune disease in which the myelin sheath surrounding motor and sensory neurones is progressively destroyed. It is the commonest neurological condition in young adults in the developed world. Symptoms result from reduced signal conductivity and vary in type and severity depending on the location and extent of myelin loss. Muscle spasticity affects ~90% of MS patients at some time and can be extremely painful. Debilitating tremor is also common. Controlling these symptoms is difficult: drugs used include baclofen, dantrolene, diazepam and tizanidine, but they are unsatisfactory for many patients because of dose-limiting side-effects.

Many sufferers find that smoking cannabis provides the best relief. Anecdotal evidence for the anti-spastic and anti-tremor effects of cannabinoids has been backed up by experiments with mouse models of MS [1]. These provided strong evidence that cannabinoid (CB) receptors are involved in the control of spasticity where there is neurological damage. CB receptors are thought to have a regulatory role in nerve signal transmission at the synapse. Blocking them makes tremor and spasticity worse, although the mechanism for this is not yet fully understood. Research has thus concentrated on developing selective CB receptor agonists that have therapeutic but not psychoactive effects.

Inhibiting spasticity

Several Phase III clinical trials are under way in the UK using natural cannabis extracts, both in MS and in other indications such a neuropathic pain and appetite enhancement. The main active ingredients in natural cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD). Other researchers are working on synthetic cannabinoids. Atlantic Technology Ventures (ATV; New York, NY, USA) has developed ajulemic acid (CT-3; see Fig. 1), a proprietary synthetic analog of the THC metabolite, THC-11-oic acid. Initially developed as an alternative to non-steroidal anti-inflammatory drugs (NSAIDs), it inhibits prostaglandin synthesis and has shown analgesic and anti-inflammatory activity in animal studies [2]. In a Phase I clinical trial it produced no clinically relevant adverse events, and no cannabis-like psychoactivity at the doses used (ATV, unpublished data). David Baker and colleagues at University College London's Institute of Neurology (London, UK) have now demonstrated that intravenous CT-3 inhibits spasticity in the chronic relapsing experimental allergic encephalomyelitis (CREAE) model of MS in mice (D. Baker, unpublished).



Drug Discovery Today

Figure 1. Ajulemic acid (CT-3), a synthetic analog of the THC metabolite, THC-11-oic acid. R indicates the absolute configuration of the chiral centers.

'CT-3 produced drastic inhibition of spasticity and limb stiffness at microgram doses, with a very rapid onset of action,' said Michael Ferrari of ATV. 'The inhibition was relatively long-lived. The

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mice tolerated very high doses of up to 50 mg kg^{-1} intravenously, without evidence of psychotropic side effects typical of CB-1 agonists. If you give mice THC at high doses they fall over.'

Mode of action

The mechanism of action of CT-3 is unknown, but unpublished research by ATV has shown that, despite its lack of psychoactivity, CT-3 does cross the blood–brain barrier. It does not have a high affinity for either of the known CB receptors, but appears to antagonize some of the actions of THC [2]. 'It is a partial CB1/CB2 agonist,' says Ferrari, 'but we think it might also be acting on a third cannabinoid receptor that has not been cloned yet.'

CT-3's analgesic and anti-inflammatory profile is similar to that of NSAIDs, but animal studies suggest it might lack their characteristic side effects [2]. In contrast to NSAIDs, CT-3 caused no gastrointestinal ulceration in mice at therapeutically relevant doses. One potential indication is rheumatoid arthritis, where CT-3 appears superior to other NSAIDs in preventing joint destruction in a rat model [2].

Future work

The development of CT-3 is going ahead on several fronts. A pilot Phase I/II study has just begun in Germany to test its analgesic properties in patients with neuropathic pain. Upon completion of further safety studies to test the higher dose limits of CT-3, a Phase II study will be carried out in tremor and spasticity in MS. The US Army Medical Research Institute for Chemical Defense is also testing CT-3 as a possible treatment for the chemical warfare blister agent sulfur mustard.

'Route of administration is a big issue with cannabinoids, and no one has really cracked it yet,' says John Zajicek, Consultant Neurologist at the Derriford Hospital (Plymouth, UK) and a principal investigator in the Cannabis in MS study for the UK's Medical Research Council. 'It is difficult to get a consistent dose orally because the high lipophilicity [of cannabinoids] leads to individual variations in absorption, and there is a lot of first-pass metabolism in the liver. Inhalation avoids that, but the technology is difficult and in some studies there has been irritation of the airways.' However, he is optimistic that cannabinoids have a therapeutic role. 'I predict that there will be a whole family of synthetic cannabinoids that will be effective in different indications, and hopefully these will have very few psychoactive effects.'

References

1 Baker, D. *et al.* (2000) Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 404, 84–87

2 Burstein, S.H. (2000) Ajulemic acid (CT3): a potent analog of the acid metabolites of THC. *Curr. Pharm. Design* 6, 1339–1345

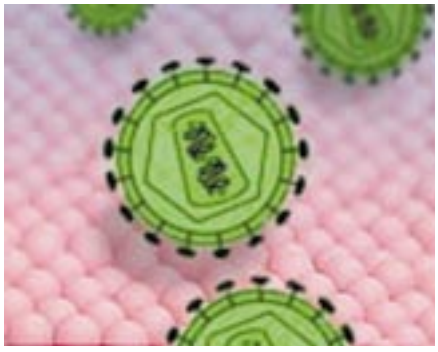
Dumped drugs could prevent HIV

Julie Clayton, freelance writer

Drugs that once held promise as treatments for HIV but were discarded because of their poor oral absorption into the bloodstream are now getting a new lease of life as potential microbicides that prevent the transmission of HIV during intercourse.

One such agent is UC781, which binds tightly to, and inhibits, the HIV replication enzyme, reverse transcriptase. UC781 failed to reach the clinic because of its poor solubility, and hence poor chance of being absorbed by the body. 'But none of those things are relevant to being able to inhibit the virus in a gel in the vagina, for example,' said Joseph Romano of Biosyn in Huntingdon Valley, PA, USA.

Biosyn obtained a license in May 2001 to develop UC781 as a topical microbicide,



one of many such products that are now being investigated for their potential action in the vagina or rectum to block HIV infection from semen.

The first 'tight binder'

UC781 was first developed as a potential fungicide by Uniroyal Chemical (now Crompton), and was one of literally thousands of compounds offered to the US National Institutes of Health (NIH) for testing against HIV. It showed impressively high activity as the first 'tight binding' non-nucleoside inhibitor of the reverse transcriptase enzyme of HIV-1. It targets the same site as nevirapine – now a commonly used systemic drug – but with a thousand-fold higher affinity, according to Israeli researcher Gabi Borkow, who was part of the original team that discovered its activity in the laboratory of Mike Parniak, at the Sir Mortimer B. Davis-Jewish General Hospital in Montreal, Canada (for review see [1]).

'Uniroyal got very excited, but when they tested for bioavailability they quickly lost interest,' said Borkow. Now at

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