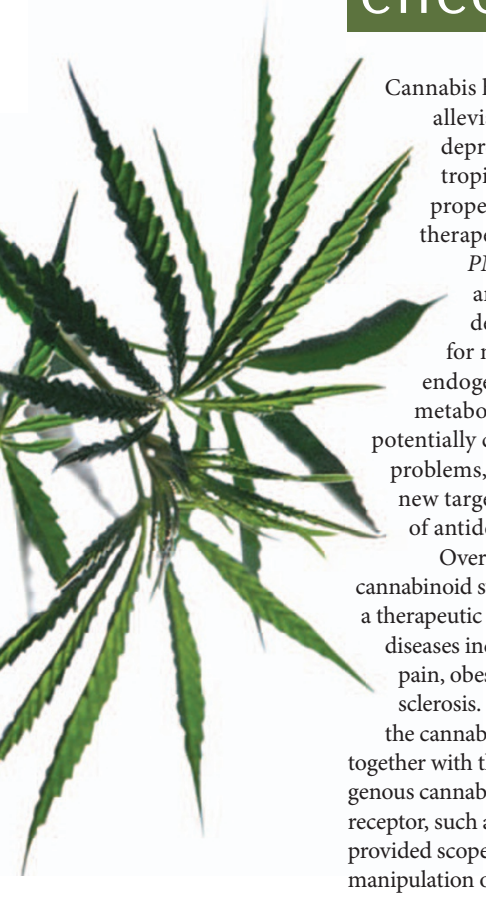
NEUROLOGICAL DISORDERS

Harnessing the beneficial effects of cannabis



Cannabis has been reported to alleviate the symptoms of depression, but its psychotropic effects and addictive properties prevent its therapeutic use. Writing in *PNAS*, Daniele Piomelli and colleagues now describe an approach for manipulating endogenous cannabinoid metabolism that could potentially circumvent such problems, thereby identifying a new target for the development of antidepressant drugs.

Over recent years, the endocannabinoid system has emerged as a therapeutic target for a range of diseases including neuropathic pain, obesity and multiple sclerosis. The identification of the cannabinoid receptor CB_1 — together with the discovery of endogenous cannabinoids that activate this receptor, such as anandamide — has provided scope for the therapeutic manipulation of this system.

The CB_1 receptor is expressed in many brain regions, including areas associated with emotional behaviour such as the hippocampus, midbrain and amygdala. Elevated endocannabinoid levels in these regions are observed in response to stressful stimuli, suggesting that endocannabinoids may have a role in coping with stress.

Indeed, direct activation of CB_1 has been reported to have antidepressant effects, but the widespread expression and diverse roles of this receptor make it challenging to separate these effects from the unwanted psychotropic actions. In a new approach to manipulate endocannabinoid signalling, Piomelli's group in collaboration with chemists at the Universities of Urbino and Parma (Italy) developed compounds which inhibit the enzyme responsible for anandamide metabolism, fatty acid amide hydrolase (FAAH). The key advantage of this approach is that anandamide is produced 'on demand' and not stored, and so by targeting its metabolism anandamide signalling is primarily affected in areas in which it is naturally up-regulated, and not in regions which produce side effects.

In previous work, the researchers demonstrated that one such compound, URB597, reduces anxiety-related behaviour. In this new study, URB597 was further characterized in two rodent models of depression, the tail suspension test and the forced swim test. In both models, URB597 treatment improved stress-coping behaviour. Furthermore, the researchers confirmed that URB597 does not produce reward-related behaviour, suggesting that such compounds would not be addictive.

To investigate the underlying mechanism, the authors measured neuronal firing in midbrain regions associated with emotional behaviour, and found increased activity of neurons which release serotonin and norepinephrine, two neurotransmitters implicated in the pathophysiology of depression. Further studies are needed to establish whether these effects are indeed responsible for the observed influences of URB597 on behaviour, and other important questions remain to be addressed, such as the effects of chronic treatment with these compounds.

Nevertheless, this study provides encouragement that drugs that target FAAH could become a new class of antidepressants. And as they activate both serotonergic and noradrenergic systems, this class of compounds might ultimately have greater efficacy than the widely used serotonin-re-uptake inhibitors (SSRIs). Furthermore, their acute anxiolytic effects could also be advantageous, given the time lag for the onset of the antidepressant action of SSRIs.

Katherine Whalley

ORIGINAL RESEARCH PAPER Gobbi, G. *et al.* Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proc Natl Acad. Sci. USA* **102**, 18620–18625 (2005)
FURTHER READING Di Marzo, V. *et al.* The endocannabinoid system and its therapeutic exploitation. *Nature Rev. Drug Disc.* **3**, 771–784 (2004)