



CANNABIS THERAPEUTICS

THE HUMAN CANNABIS FARM

Cannabis smokers have been indirectly responsible for important developments in nervous system medicine. **Richard Shrubb** on how the body's own cannabinoids have the potential to treat a range of conditions, including psychosis.

You will probably be aware that the body makes its own opiates, such as endorphins. But it also makes its own cannabis too – endocannabinoids (ECBs). ECBs were discovered in the 1960's when scientists asked the question: why do people get stoned from smoking marijuana? New types of neurotransmitters, chemicals that pass messages between nerve cells, were found which were similar to the psychoactive elements of cannabis. They named the neurotransmitters after the cannabis plant – the word

'endocannabinoid' literally means 'the body's internal cannabinoid'.

The introduction to a series of papers published in the *Philosophical Transactions of the Royal Society* last year suggested that the ECB system affects a huge range of functions in the brain and body. It said: "Among other functions, the [ECB system] is involved in...regulation of motor activity,...synaptic plasticity and the control of certain phases of memory processing." Synaptic plasticity (synapses are the gaps between nerve cells) has a bearing on illnesses such as psychosis,

multiple sclerosis and dementia because of its influence on motor control and memory processing.

Professor Maurice Elphick, a neurophysiologist at Queen Mary and Westfield College, University of London says the ECB system is a primeval one, active long before we came out of the trees. "Endocannabinoids evolved in animals very early – perhaps 500 million years ago. Humans have it, but so do very basic animals such as sea squirts." There are only two receptors in the ECB system, CB1, found mainly in the brain and CB2,

predominantly found in the body.

ECBs are not the same as other neurotransmitters, such as dopamine, in that they travel both ways through the synapse. Experts describe them as "synaptic moderators", which control the amount of neurotransmitter chemicals that pass across the synapses. If you are able to accelerate or stop messages being passed through the gaps between neurons, you can control a variety of functions throughout the brain and body.

The weight loss medication rimonabant uses the ECB system. It works by blocking the reception of the body's two ECBs, anandamide (ananda is Sanskrit for bliss) and 2AG. But doctors found that in some cases the drug had a downside, leaving a number of people feeling suicidal, because of the fact their brains were denied the ECBs.

The reward element of the ECB system is now being closely associated by scientists to what is commonly known as a 'runner's high', the feeling of intoxication felt after a long, hard spell of exercise. Until recently, this high was thought to have been down entirely to endorphins, the body's own opiates. But a 2004 paper found links between runner's high and the ECB system. The study, published in the *Journal of Sports Medicine*, found concentrations of anandamide in the blood after exercise.

A lot of work has gone into using cannabis as a pain reliever. Anecdotally, people report much greater benefit from using cannabis to relieve pain than opiates. Not only are opiates addictive, their effects wear off over time, meaning you need more and more to achieve the same pain relief. Opiates used over a long period can become debilitating in their own right, while cannabis does not appear to have the same drawbacks.

GW Pharmaceuticals is in late stage trials to use its Sativex cannabis spray on patients suffering cancer pain. Now, 15 US states allow the use of marijuana to combat a range of medical conditions. Sativex is licensed in the UK to combat muscle cramps from multiple sclerosis – this is thought to use CB2 receptors affecting motor control.

Mental health conditions such as schizophrenia are some of the most difficult conditions to treat as they affect the way someone perceives the world. Research into ECBs has resulted in a potential treatment for schizophrenia.

Scientists found that although the psychoactive compound of cannabis, THC, can cause psychosis, another cannabinoid from cannabis, cannabidiol (CBD), can act as an antipsychotic.

In a study published in the *Journal of Translational Psychiatry* in March last year CBD was given to a group of patients suffering psychosis, in a direct comparison to a licensed antipsychotic called amisulpiride. The results were very promising, concluding: "Either treatment was safe and led to significant clinical improvement, but cannabidiol displayed a markedly superior side-effect profile."

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The findings surprised clinicians in this line of research, because unlike traditional antipsychotics, that exploit the dopamine synaptic system, CBD uses the ECB system. The study said that CBD "does not activate cannabinoid receptors, but moderately inhibits the degradation of the endocannabinoid anandamide." In short, CBD doesn't bind to synapses, but raises the amount of the body's own cannabinoids by preventing them from being broken down. A higher amount of ECB chemicals in the system is therapeutic for a range of illnesses. Dr Paul Morrison of Kings College London says CBD affects psychosis because it affects mental plasticity. "Failure of the highest functions such as the will, object perception, thinking, beliefs and self-other differentiation is the essence of major mental illness. To that we must accommodate how assemblies and synapses change over time, according to the information they process. This is the concept of plasticity. ECBs are vital for assembly dynamics and for plasticity."

He says the chief issue faced in

cannabinoid research is intoxication: "The challenge is to develop molecules which have an absence of [central nervous system] effects." Giving cannabis to a patient will involve getting them intoxicated on THC, and though it helps with symptoms, no one wants to be stoned all day.

And Professor Val Curran, a psychopharmacologist at Imperial College London, points out an added value of CBD as an antipsychotic: "it does not entail the weight gain or side effects associated with more commonly used antipsychotic drugs".

Pharmaceutical research is looking at regulating levels of ECBs in the system rather than adding plant cannabinoids. But, as was seen with rimonabant, this hasn't always been successful. CBD seems to prevent psychosis not by attaching itself to receptors and intoxicating the patient but by preventing the breakdown of anandamide in the body. So does more anandamide equal less psychosis? This certainly seems to be the case.

If you're feeling down and depressed, should you then smoke a joint to "top up your endocannabinoids" as one or two people have suggested to me? The answer from the experts is emphatically no. "We have research, yet to be published, that suggests cannabis users reduce their endocannabinoid levels," says Prof Curran. "This is likely because the brain has its own homeostasis. Like a rainforest, it will try to balance itself out."

If you smoke cannabis regularly, your brain will reduce the amount of endocannabinoids it produces, or reduce its sensitivity to them. THC, for instance, causes psychosis in cannabis users, having altered the plasticity of the brain by interfering with the homeostasis or chemical balance inside it.

Ten years of intensive research into a field of brain science is a very short time. For example, it isn't fully understood exactly what current antipsychotics, those affecting the dopamine pathway, actually do to make people well. The idea that the ECB system can be used for therapeutic benefit is beyond doubt, but a fuller understanding of the system is a fair way off.

■ **Richard Shrubbs** is a freelance journalist