Where has our knowledge of drugs and the brain come from?

As scientists, it is useful for us to know where our knowledge has come from as this helps us assess how much we should trust it. The history of cannabis research serves to illustrate how scientists have used many different methods, each with its own strengths and weaknesses, to develop our understanding of recreational drugs.

When cannabis was studied by pharmacologists in the 1950s and 60s it was found to contain a number of different compounds but it was not clear which of these were responsible for the psychoactive effects of the drug. Edery et al (1971) tested these different compounds by giving varying doses of each to rhesus monkeys and observing their behaviour. Some of the compounds had no effect, and one had an effect rather like the one observed in humans: drowsiness, stupor, lack of co-ordination and suppression of motor activity. This led Edery et al to conclude that the active component in cannabis and marijuana is Δ9-THC. However, they could not be certain that the monkeys experienced the same subjective effects as humans and, in fact, it was not guaranteed that Δ9-THC was the same compound that is psychoactive in humans. Neither did the study tell us how Δ9-THC affects the brain.

Subsequently, Devane et al (1988) tested the effects of Δ9-THC on neurons from mice, grown in the laboratory. The way the cells reacted when exposed to Δ9-THC alongside other drugs indicated that the neurons contained a post-synaptic receptor to which the drug could bind. Devane et al concluded that the mouse brain contains a type of synapse that is influenced by cannabis compounds. They called it CB1. However, this finding did not tell us whether the same receptors were present in the human brain, where they might be located if they were present or how they produced their effects on thinking and behaviour.

The existence of a synaptic receptor specific to cannabis-like compounds suggested to researchers that the brain must be producing its own neurotransmitter whose job it is to bind to the CB1 receptors. Devane et al extracted brain tissue from pigs and used chromatography to separate out its contents. Among them, they found a neurotransmitter with an affinity for the CB1 receptor. They named this neurotransmitter ‘anandamide’. The presence of CB1 receptors in mice and pigs suggested strongly that the same receptor and neurotransmitter would be present in the human brain but not not guarantee that it was. Munro et al (1993) used polymerase chain reaction (PCR) to isolate genes from human neurons grown in the lab. Among them were some that looked very similar to genes that code for the CB1 receptor in rats. Munro et al cloned these receptors and tested them with cannabinoid compounds, finding that these receptors had a strong affinity for Δ9-THC. This showed that the anandamide receptor was present in the human brain and that it was responsive to the active compounds found in cannabis.

Mathew et al (1997) used PET to investigate cerebral blood flow (i.e. blood flow to different parts of the brain) in 32 human volunteers. The participants were injected with Δ9-THC or a placebo drug whilst they were scanned. It was a double blind study, so neither the participants or the researchers knew who was getting the drug and who the placebo. There was an increase in cerebral blood flow to the frontal lobes in those who had received the Δ9-THC. This shows that Δ9-THC has a specific effect in brain activity in humans, although it does not tell us exactly how those changes result in the altered experiences of Δ9-THC users. More recently, Hirvonen et al (2011) used a special radiotracer that binds to the CB1 receptors in the human brain. They recruited some regular marijuana users and some non users and compared them in a PET scanner. They found that the marijuana users had around 20% fewer CB1 receptors throughout their brain than the non-users. Those who had been using the longest showed the greatest reduction in CB1 receptors. This shows that long term consumption of Δ9-THC by humans has a direct effect on anandamide receptors in the brain.

These are just a few of the studies that have helped us as scientists to understand how one drug affects the brain. Collectively, they also show how scientific knowledge develops over time, how scientists think critically about the research they do and how new methods are adopted to overcome the limitations of old ones.