

COMMENTARY

Towards a better cannabis drug

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Keywords

cannabidiol,
 Δ^9 -tetrahydrocannabinol, CBD,
THC, cognition, learning,
memory, cannabis, sensorimotor,
motivation

Received

22 August 2013

Accepted

5 September 2013

This commentary discusses the importance of a new study entitled 'Cannabidiol attenuates deficits of visuo-spatial associative memory induced by Δ^9 -tetrahydrocannabinol' by Wright *et al.* from the Scripps Institute in La Jolla, California. The results in this study show that the non-psychoactive cannabis constituent cannabidiol opposes some, but not all, forms of behavioural and memory disruption caused by Δ^9 -tetrahydrocannabinol in male rhesus monkeys.

LINKED ARTICLE

This article is a commentary on the research paper by Wright *et al.*, pp 1365–1373 of this issue. To view this paper visit <http://dx.doi.org/10.1111/bph.12199>

Abbreviations

CBD, cannabidiol; THC, Δ^9 -tetrahydrocannabinol

Opium smoking has been mostly replaced by i.v. injection of morphine and heroin, and we see cocaine sniffing rather than chewing of coca leaves. Cannabis use – be it of marijuana, hashish or bhang – differs. Any cannabis *cognoscente* will insist that the crude material is 'much better' than pure Δ^9 -tetrahydrocannabinol (THC), the only major psychoactive constituent of cannabis (Mechoulam *et al.*, 1970). Indeed, although pure THC is available as a drug (named dronabinol) it is apparently not used illicitly. The pharmacological/biochemical basis for this difference is not clear and is presumably due to several factors. A major reason seems to be the pharmacokinetic difference between cannabis smoking and the oral administration of THC. On smoking, the cannabis effects are noted almost immediately, while a 1.5–2 h delay is observed on oral administration. A further factor may be conditioning to the smell, although there are no published data along these lines. A further factor may be the presence of the terpenoid CB2 agonist beta-caryophyllene in cannabis (Gertsch *et al.*, 2008). CB2 agonists are well known to cause numerous effects (mostly of a protective nature), which may counteract some of the effects of THC (Pacher and Mechoulam, 2011).

However, the only well-established biochemical factor for the difference between THC and crude cannabis seems to be

the presence of the cannabis constituent cannabidiol (CBD) in some cannabis strains. CBD by itself does not cause any THC-like psychoactivity, but it has anti-anxiety, anti-epileptic, anti-nausea and anti-schizophrenic properties (Mechoulam *et al.*, 2009). CBD has been shown to alter THC activity. Over 30 years ago Brady and Balster (1980) reported that CBD antagonizes the effects of THC on operant behaviour in rhesus monkeys. More recently it was reported that while acute intoxication with cannabis, with high levels of THC and low levels of CBD, or pure THC, impairs cognitive function, the cannabinoid spray Sativex (a 1:1 ratio of CBD:THC) at low doses reduces some of the effects produced by THC, including subjective ratings of intoxication, cognitive impairment and abuse/dependence (Wade *et al.*, 2004; Robson, 2011; Schoedel *et al.*, 2011).

Recent studies in humans have shown that smoking CBD-enriched marijuana does not lead to deficits of prose recall that are caused by CBD-poor cannabis. Furthermore, users of CBD-rich cannabis have better preserved recognition memory, compared with users of CBD-poor cannabis (Morgan *et al.*, 2010; 2012). However, conclusions based purely upon studies of current cannabis smokers are inherently limited by the possibility that characteristics of people who prefer CBD-rich cannabis may differ from those of

people who prefer CBD-poor cannabis. Experimental verification in non-human primates that CBD can oppose the cognitive impairing effects of THC is presented in this issue of the journal (Wright *et al.*, 2013).

Taffe (2012) has previously shown that in monkeys, THC impairs spatial working memory, consistent with research in rodents showing that spatial working (short term) memory is much more vulnerable to disruption by THC than is reference (long term) memory (Mechoulam and Parker, 2013). In the present paper, the same group presents direct evidence that CBD can oppose the cognitive impairing effects of THC in the visuo-spatial paired associate task that involves both spatial working memory and pattern recognition. Although CBD did not reverse the memory-impairing effects of THC in a non-associative spatial memory task, the self-ordered spatial search task, the effect of THC did not increase with task difficulty, suggesting a sensorimotor rather than a mnemonic effect of THC on that task. In an operant learning task designed to assess motivational persistence in responding, the progressive ratio task, CBD did not reverse the impairment produced by THC. Together, these findings suggest that CBD protects against the mnemonic deficits, not the motivational deficits, produced by THC. Interestingly, CBD also protected against the motoric impairments produced by THC in a task requiring ambidexterity, but not in a unimanual motor task. In summary, CBD opposes some, but not all, forms of behavioural and memory disruption by THC.

The reversal by CBD of some of the undesirable effects produced by pure THC or by cannabis with low levels of CBD and high levels of THC, as shown by several investigators and now by the Scripps group, strengthens the view that medicinal cannabis containing reasonably high levels of CBD is a better drug than cannabis with low levels of CBD or pure THC alone.

Conflict of interest

We have no conflict of interest to report.

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