Editorial

Original version accepted in English

Effect of cannabis use in human brain activity

Efeito do uso de maconha na atividade cerebral humana

While Marijuana (*Cannabis sativa*) has been used recreationally and medicinally for thousands years, over the last decades there has been a steady increase in the consumption of cannabis in many countries, especially among young people. This rising prevalence has caused concern. First, because cannabis use might lead on to the use of other more harmful illegal drugs, such as heroin and cocaine. Second, recent evidence indicates that early and regular cannabis use increases the risk of poor educational performance, early school drop-out, and depression, anxiety and psychosis in later life.[1]

Although research on the mental health effects of cannabis has increased dramatically, our knowledge of its effect on the brain is still limited. *Cannabis sativa* is a plant comprising 400 different identifiable chemical constituents, more than 60 of which are cannabinoids. The two main cannabinoids are delta-9-tetrahydrocannabinol (D9-THC) and cannabidiol (CBD). Cannabinoids exert their effect by interaction with specific endogenous cannabinoid (CB) receptors. The latter involve membrane phospholipids and G-proteins. The CB1 receptor is expressed throughout the central nervous system whereas CB2 expression seems restricted to immune cells. Binding to CB1 receptors has effects on second messenger cascades as well as on ionic membrane conductance. Endocannabinoids may modulate glutamate and GABA synaptic transmission and can have postsynaptic effects on dopamine transmission. The endocannabinoid system has been implicated in a large variety of physiological central functions such as motor behavior, learning and memory, emotion, reward, food intake, neuroprotection, nociception, and some vegetative and peripheral responses.[2]

The way that D9-THC and CBD act on the brain remains unclear. D9-THC receptors are densely distributed in the basal ganglia, cerebellum and frontal cortex, suggesting a role for cannabinoid receptors in motor control, and consistent with the effects of cannabis on motor performance. Cannabinoid receptors in paralimbic cerebral cortex (including hippocampus and amygdala) may mediate the effects of cannabis on cognitive and emotional functions in humans. The receptors that mediate the psychological effects of CBD are still unknown. CBD does not bind to the central known cannabinoid receptor, CB1[3] and its effects may be unrelated to THC-type activity.

Neuroimaging techniques, including functional neuroimaging, provide a powerful means of investigating the central actions of cannabis in man, in vivo. To date there have been few neuroimaging studies of the effects of D9-THC. In this issue of Revista Brasileira de Psiquiatria, Crippa et al[4] review neuroimaging research on cannabis. Results from structural neuroimaging studies have so far been inconclusive, perhaps due to methodological problems (few studies, small samples, poly-drug users, and inclusion criteria). Most of the functional imaging studies have used FDG-PET or SPECT, techniques with a relatively poor spatial and temporal resolution, and have examined activity during the "resting state", making it difficult to link the activity with specific cognitive or emotional processes. These studies have reported changes in anterior cingulate, frontal temporal and cerebellar cortex. There has only been one neuroimaging study of CBD to date, and this indicated that CBD altered resting activity in limbic and paralimbic brain areas. Three studies of cannabis using fMRI have been published. One reported that long-term cannabis users showed greater anterior cingulate and prefrontal activation than controls did when performing a spatial working memory task. Another pilot study in adolescent users of cannabis and nicotine during a working memory task showed reduced hippocampal activation relative to controls. Lastly, a study in young adults of the effects of prenatal exposure to cannabis suggested that it has an impact on the activation of brain areas engaged during a Go/No-Go task.

Crippa et al[4]'s review highlights some of the limitations of the research done to date and the need for further investigation. Cannabis misuse, like other psychiatric disorders, involves a complex interaction between biological (genes, protein expression, neuronal circuits) and environmental factors (cannabis, others drugs, family and social background). Functional neuroimaging could be used to characterize the brain areas involved in the different states of the cannabis abuse/dependence disorder (intoxication, withdrawal and craving), as has been done for other substances.[5] It is also possible to use functional imaging to study the modulatory effect of cannabis on brain activation during cognitive tasks engaging cognitive processes that appear to be affected by cannabis use, such as memory and motor function. Neuroimaging can also be used to assess the impact of gene polymorphisms (e.g. COMT) on protein expression and brain function. On the other hand, recent pharmacological research has led to the synthesis of cannabinoid receptor agonist and antagonists, endocannabinoid re-uptake blockers and selective inhibitors of endocannabinoid degradation. Some of them might be new tools for study the cannabinoid receptors, cannabis and endocannabinoid brain activity or future treatments.

Rocío Martín-Santos
Section of Neuroimaging, Institute of Psychiatry, King's College, London, Great Britain
Pharmacological Research Unit, Institut Municipal d'Investigación Mèdica, Barcelona, Spain

Zerrin Atakan and Philip McGuire
Section of Neuroimaging, Institute of Psychiatry, King's College, London, Great Britain

References

1. Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. Br J Psychiatry. 2004;184:110-7.
2. Rodriguez de FF, Del A, I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: physiology and pharmacology. Alcohol Alcohol. 2005;40(1):2-14.
3. Menchoulam R, Hanus L. Cannabidiol: an overview of some chemical and pharmacological aspects. Part I: chemical aspects. Chem Phys Lipids. 2002;121(1-2):35-43.
4. Crippa JA, Lacerda ALT, Amaro E, Busatto G, Zuardi AW, Bressan RA. Brain effects of cannabis: neuroimaging findings. Rev Bras Psiquiatr. 2005;27(1):70-8.
5. Volkow ND, Fowler JS, Wang GJ. The addicted human brain: insights from imaging studies. J Clin Invest. 2003;111(10):1444-51.