HOW DOES MARIJUANA WORK IN THE BRAIN?

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Building upon last month's review of the endocannabinoid system (Buckland & Cunningham, 2013), we now take a closer look at marijuana, which, according to the National Institute on Drug Abuse, is the most commonly used illegal and addictive drug worldwide (http://www.drugabuse.gov/drugs-abuse/marijuana). Unfounded scare tactics from the early 1900s, as well as social acceptance for this drug, have created a false sense of security regarding its use. How does marijuana work in the human brain, and are there reasons for concern?

Marijuana is usually smoked, so it reaches the brain quickly and its effects can last for a couple of hours. Cocaine and amphetamine act directly on dopamine (DA) nerve terminals, leading to euphoria; whereas opioids, ethanol, and marijuana act on receptors located on GABA nerve terminals to increase dopamine levels. The psychoactive ingredient in marijuana is tetrahydrocannabinol (THC), though marijuana contains hundreds of other known compounds, not as well researched as THC. THC works by binding to the same receptors that our endogenous endocannabinoids utilize, CB1 and CB2. Remember that CB1 receptors are found on the presynaptic nerve terminals, which contain the primary inhibitory and excitatory neurotransmitters, GABA and glutamate. The distribution of CB1 and CB2 receptors changes over the course of development; they are more plentiful in the developing brain and less plentiful in the adult brain (Machoulam & Parker, 2013). As a result, there are more opportunities for THC to bind in nonadult brains.

THC is biphasic, meaning that effects of low dosages (relaxation and euphoria) are opposite those of high dosages (delirium and "madness") (Mechoulam & Parker, 2013). However, biphasic actions do not occur simply in relation to different dosages of THC. Solinas et al. (2007) reported in animal studies that methods used to evaluate the reward properties of a drug may actually determine the outcome. For most reinforcing drugs, the method *conditioned place preference* (teaching an animal to make positive associations with the location of administration of a drug), works well. With THC, depending on the conditions of the experiment, one may get either conditioned place preference or *conditioned place aversion* (i.e., positive or negative effects of the drug).

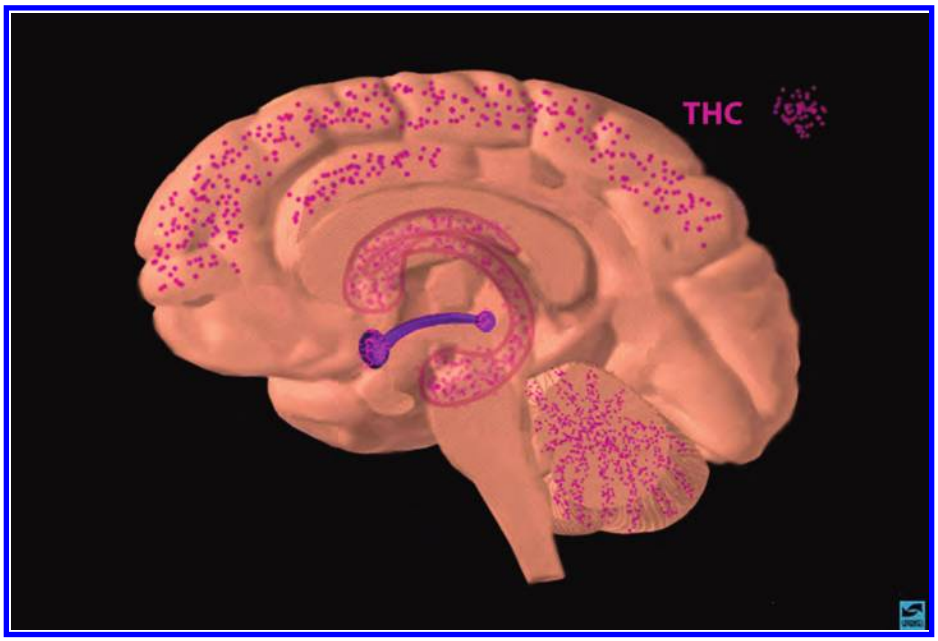

Figure 1. Dots represent areas where THC binds in the human brain: frontal and limbic areas (top and center), ventral tegmental area (represented by the bold bar), and cerebellum (bottom right). (Figure courtesy of Rochelle D. Schwartz-Bloom and adapted with permission from the National Institute on Drug Abuse: http://www.drugabuse.gov/publications/teaching-packets/brain-actions-cocaine-opiates-marijuana/section-iii-introduction-to-drugs-abuse-cocaine-opia-10.)

Although changes in the cardiovascular (increased heart rate and blood pressure) and reproductive systems (suppression of sexual function and reproduction) due to THC have been documented, evidence for these changes having significant impact is controversial. However, the impact of THC on the central nervous system is clear. Because cannabinoid receptors are abundant in frontal and limbic portions of the brain, marijuana use can affect the senses, mood, learning, memory, motivation, motor control, reward processing, and executive functions (see Figure 1). THC decreases one's ability to use episodic, retrieval-based and working memory; decreases inhibition; and increases impulsivity (Crane et al., 2012).

New research, specifically in relation to adolescents, indicates a significant impact of cannabis use on the central nervous system. Meier et al. (2012) led a prospective longitudinal study conducted in Dunedin, New Zealand, to review intellectual effects in

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>1000 study participants over a 25-year period. Neuropsychological testing was administered to participants at age 13, and interviews occurred at regular intervals until age 38, when the testing was repeated. Those who initiated cannabis use in adolescence and developed cannabis dependence before age 18 exhibited an eight-point decline in IQ, which was not restored with cessation of use. Those who initiated use in adulthood did not show this decline (Meier et al., 2012). This IQ decline is significant; in an interview (Harrison, 2012), M. H. Meier commented that for a person with an average IQ, this drop is the same as going from the 50th to the 29th percentile in intelligence. This change could have an impact on future educational and job performance. Although a recent analysis of the study results suggests that these results may be premature, the results have not been discredited (Rogeberg, 2013).

The potential and considerable impact of persistent marijuana use on adolescents gives cause for reflection. A mind is a terrible thing to waste! Looking ahead to next month, we'll return to the reward pathway and dopamine as we consider the diverse ways in which stimulants interact with that pathway and the potential short- and long-term effects.

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