The Brain's Endocannabinoid System: An Overview

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In order to understand how marijuana creates its typical "high," how it might serve as a medication and how it changes normal brain function when used too regularly, it is necessary to understand the brain's natural marijuana-like chemistry.

All animals with even the most basic neural network, even before central nervous systems (i.e., brains) evolved, use molecular messengers that are mimicked by marijuana. The THC in marijuana so closely resembles anandamide (one of our brain's endogenous neurochemicals) that our cannabinoid receptors (called CB1 receptors) cannot distinguish between the two. Smoking marijuana sends THC into the blood and up to the brain where it stimulates our endogenous cannabinoid system far beyond normal.

Most facets of the experience of acute marijuana intoxication can be explained as altered activity in specific portions of the brain that contain high concentrations of the CB1 receptor. Losing short-term memory comes from stimulation of CB1 receptors in the hippocampus. Relaxation, increased appetite, a feeling of novelty attached to many sensations and a general sense of awe all stem from stimulation of CB1 receptors in the amygdala. We now understand that the "magic" does not lie in the herb, but rather in our brain.

Neuroscience research is working to discover the normal function of our endogenous cannabinoid chemistry. Most neurotransmitters are released when a nerve cell fires, travel across a gap to the next nerve cell down the line, and then stimulate their unique receptor on the next nerve cell. Anandamide goes in the opposite direction. It travels back across the gap to the initial nerve cell to modify its behavior. Our natural cannabinoids balance the entire rest of brain chemistry, keeping all other neurotransmitters from being over-or under-active. Cannabinoids have therefore been described as neuro-regulators.

The overall modulation of brain activity provided by our natural endogenous cannabinoid system can be driven far from its normal equilibrium in two ways. In the short-term, the THC from marijuana stimulates all CB1 receptors to non-physiologic levels. This is enjoyable for most people. Increased activity in the cannabinoid system may also correct imbalances caused by some illnesses, reducing pain and increasing appetite, among other potential benefits.

But the brain is naturally a conservative system. Like all biologic organisms, it attempts to return to its normal balance (known as homeostasis). The adaptive reaction to regular use of marijuana is to hide and then dismantle some of the CB1 receptors. After a couple of weeks of heavy stimulation from smoking marijuana, areas of the brain have 20-60% fewer cannabinoid receptors. People can usually still get "high" because marijuana provides enough THC to activate every available receptor, which THC stimulates more strongly than anandamide does.

Difficulty arises when the THC from marijuana dissipates, leaving the normal amount of anandamide with fewer than normal receptors to stimulate. The result is a state of relative cannabinoid deficiency. Appetite is reduced rather than stimulated. Experience is more boring than novel. Restlessness replaces calm. This is the basis for symptoms of withdrawal from marijuana. What went up at first now must come down.

THC also stimulates the same motivational center that all other addictive drugs activate. Regular use over time intensifies the brain's drive to repeat the experience, which can contribute to dependency risks and difficulty in stopping use.

A critical additional wrinkle is added when the user of marijuana is an adolescent. The brain experiences a burst of new growth in connections among nerve cells at puberty. Maturation consists of the proper strengthening and pruning of these new synaptic connections. Balanced functioning of the natural cannabinoid system is an important contributor to processes of brain maturation throughout adolescence. Pushing the endogenous cannabinoid system out of balance, alternating between excessive and deficient activity, by regular use of marijuana during adolescence can potentially derail some aspects of normal neurodevelopment.

Significant research is underway under National Institute of Health and other auspices to more clearly characterize the impact of chronic use in adolescence.