The Buzz on Booze

Alcoholism and the Endocannabinoid System

By Martin A. Lee

An Evaluation of Brain Endocannabinoid Signaling and Addiction-Related Behaviors
Larry Parsons, Plenary Lecture, International Cannabinoid Research Society Meeting, July 10, 2009

Endocannabinoid Signaling in Neurotoxicity and Neuroprotection
By C. Pope, R. Mechoulam, L. Parsons, *Neurotoxicology,* Dec. 4, 2009

Cannabis as a Substitute for Alcohol and Other Drugs
By Amanda Reiman. *Harm Reduction Journal,* Dec. 3, 2009

Marijuana is SAFER
By Steve Fox, Paul Armentano, Mason Tvert, Chelsea Green. White River Junction, VT, 2009. 209 pp., $14.95.

A grapevine and a cannabis plant are depicted side-by-side on a bas-relief from a ruined Roman temple at Baalbek in Lebanon's fertile Bekka Valley. One of the world's sweet spots for growing cannabis, this region is also known for its fine wines. It is a place where wine and hashish mix geographically as well as culturally.

Poets and thinkers in the Muslim world have long debated the virtues and pitfalls of alcohol and marijuana. An epic poem written by Muhammad Ebn Soleiman Foruli, a 16th century Turkish poet from Baghdad, portrays a dialectical battle between wine and hashish. The two inebriants engage in an allegorical fencing match as the poet describes the euphoric properties of both substances and their consequences, a subject much discussed among Muslim scholars. Foruli viewed wine as the drink of the rich, "while hashish," he said, "is a friend of the poor, the Dervishes and the men of knowledge."

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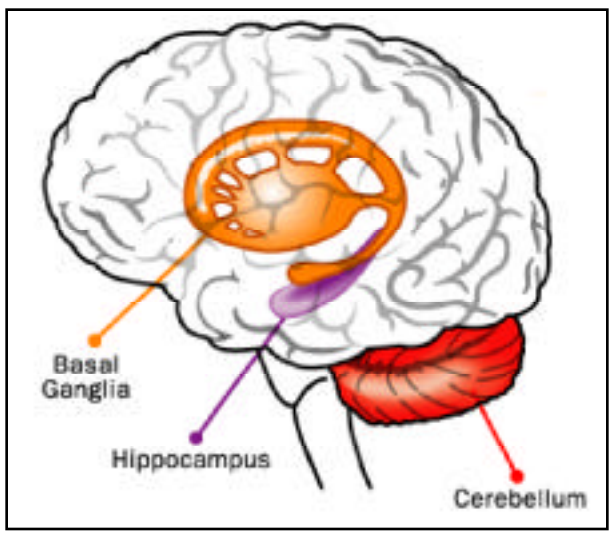
The struggle between weed and wine continues to unfold in 21st century America, where the alcohol industry funds organizations that seek to maintain marijuana prohibition. Such influence-peddling by Booze, Inc. is not only a preemptive strike against a recreational competitor; drug war posturing is also smooth public-relations for liquor companies given the well-documented, deleterious health and social costs of their products. Alcohol is a pivotal factor in some two-thirds of all cases of violence between intimates in the United States, and booze is responsible for 100,000 sexual assaults among young people each year and 100,000 annual deaths.

While the harmful effects of alcoholism are well known, scientists have only recently begun to investigate and understand the critical role that the endocannabinoid system plays in alcohol addiction and various mood disorders. According to several studies, ethanol exposure alters endocannabinoid levels in different regions of the mammalian brain. In a plenary lecture at the 2008 International Cannabinoid Research Society conference, Larry Parsons, Associate Professor at the San Diego-based Scripps Research Institute, discussed fluctuating endocannabinoid levels in the nucleus accumbens of ethanol-exposed rats. The nucleus accumbens is a section of the brain that mediates the pleasurable properties of certain addictive psychoactive substances. In vivo microdyalisis of the nucleus accumbens in ethanol-exposed rats disclosed that the amount of 2-arachidonoylglycerol (2-AG, the most prevalent endocannabinoid in the brain) increased and decreased in direct proportion to the amount of ethanol consumed.

Scientists believe that alcohol has a dose-dependent effect on 2-AG levels in humans as well as rodents. In other words, when a person gets a little tipsy from drinking booze, his or her 2-AG levels rise slightly; when someone gets drunk, a lot of 2-AG sloshes around the brain; and as inebriation fades, 2-AG returns to its normal, baseline level.



CANNABINOID RECEPTOR SITES ABOUND in regions of the brain including the basal ganglia (movement control), cerebellum (coordination), and hippocampus (learning and memory, stress).

Parsons and a team of researchers also documented that heroin administration triggered a corresponding rise in anandamide (the other key endocannabinoid) in the rats' nucleus accumbens, but had no effect on 2-AG levels.[1] Anandamide and 2-AG both activate the all-important CB1 receptor, which is concentrated in the mammalian brain and central nervous system. The CB1 receptor is associated with psychoactivity when stimulated by THC or synthetic cannabinoid agonists. THC also stimulates CB2 receptor signaling, but this does not result in the psychoactive buzz that cannabis is famous for; THC binding to CB1 does the trick.

Parsons's findings —which were initially reported in the *Journal of Neuroscience*[2]— raise intriguing questions regarding the causes of alcoholism and drug addiction. Is it possible that the pleasurable effects from alcohol consumption are partly attributable to higher levels of 2-AG and CB1 activity? Why does the endocannabinoid system kick into high gear when a person drinks booze? Do genetic mutations contribute to alcoholic proclivities and skewed endocannabinoid signaling in the brain?

Ethanol is metabolized into acetaldehyde, a carcinogen and a mutagen that causes many harmful effects in vital organs. Simply put, alcohol is poison, and science has shown that the basic function of the endocannabinoid system is protective in nature: hence the spike in 2-AG in the nucleus accumbens during ethanol exposure.

High 2-AG levels are also triggered by strokes and other traumatic brain injuries, according to a recent article in *Neurotoxicology,* which concluded that the endocannabinoid system "has neuroprotective properties." It can be viewed as part of the body's "general protective network, working in conjunction with the immune system and various other physiological systems."[3]

The human brain is a delicate organ, stoutly defended by a thick skull and a blood-brain barrier primed to keep foreign substances from penetrating. The endocannabinoid system is a crucial component of the brain's overall protective apparatus. Parsons put it this way: "Endocannabinoids buffer stress... An increase in endocannabinoid levels serves as a buffer to physiological and behavioral stress."

Parsons did not comment on the stress-buffering qualities of phytocannabinoids. In 2009, the journal *Neurotoxicology and Teratology* presented clinical data indicating that compounds in marijuana helped to "protect the human brain against alcohol-induced damage."[4] This study, conducted at the University of California in San Diego, found that adolescents who smoke marijuana may be less susceptible to brain damage from binge drinking.

Five years earlier, researchers at the National Institute of Mental Health demonstrated that cannabidiol (CBD), a significant nonpsychoactive component of marijuana, functioned as an "in vivo neuroprotectant ... in preventing binge ethanol-induced brain injury." CBD reduced alcohol-induced cell death in the hippocampus and the etorhinal cortex of the brain in a dose-dependent manner by 60 percent.[5]

Vomiting due to excessive intake of alcohol can be seen as another example of the protective function of the endocannabinoid system, which controls nausea and emesis. Severe vomiting associated with binge drinking is the body's way of protecting itself by expelling poison. Fifty million Americans, including nearly half of America's college students, engage in binge drinking, according to a survey by the Harvard School of Public Health. Fifteen million Americans —10 percent of the adult population— are either addicted to or seriously debilitated by alcohol.

Whereas acute alcohol exposure increases endocannabinoid levels in the brain, chronic alcohol use results in a systemic decline in endocannabinoid signaling and deficient endocannabinoid baseline levels. Parsons and co-workers report that prolonged ethanol exposure causes "diminished CB1 receptor expression," less efficient CB1 receptor binding activity and "reduced baseline extracellular 2-AG levels in the amygdala."[6]

Repeated alcohol consumption also desensitizes and weakens CB1 receptor function in the brain region known as the ventral striatum. Dysfunction of CB1 signaling in the ventral striatum correlates with increased vulnerability to alcohol addiction and suicidal tendencies. Writing in the *Journal of Psychiatric Research*, Yarahudri Vinod and colleagues proposed that pharmacological agents which "modulate the endocannabinoid tone or CB1 receptor function might have therapeutic potential in the treatment of alcohol addiction and prevention of suicidal behavior."[7]

Alcohol dependence is linked to down-regulation of 2-AG and CB1 brain receptors.

Long-term alcohol abuse depletes endocannabinoid tone, and this, in turn, has an adverse impact on a plethora of physiological processes that are modulated by the endocannabinoid system. The endocannabinoid system interacts with other neurotransmitters (serotonin, dopamine, glutamate, etc.) involved in the regulation of mood, fear, and impulsive behavior. Endocannabinoid deficiency is associated with a reduced ability or inability to adapt to chronic stress, a systemic dysfunction that becomes more pronounced during alcohol withdrawal. Alcohol dependence is linked to the down-regulation of 2-AG and CB1 brain receptors. Prolonged alcohol exposure induces deficits in the brain's endocannabinoid signaling, which, in turn, contributes to maladaptive stress coping and a renewed desire for booze consumption in a self-destructive attempt to boost CB1 receptor activity. The vicious cycle of addiction feeds on itself.

Given that endocannabinoid signaling is implicated in the behavioral and biochemical processes underlying alcohol addiction, some scientists thought that it might be possible to treat alcoholism by blocking the CB1 receptor in order to interrupt the brain's drug reward pathway. It was a harebrained theory that never panned out in the lab. Far from being efficacious for alcoholics, the administration of a CB1 receptor antagonist would block the brain's crucial neuroprotective response during alcohol

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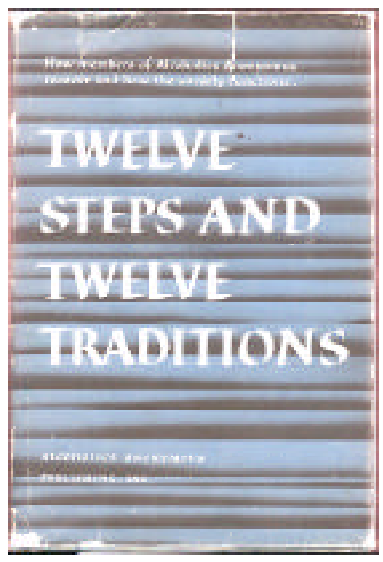

ALCOHOLICS ANONYMOUS defines recovery in terms of abstinence from all illicit substances, including cannabis.

Martin A. Lee is writing a social history of cannabis. He is the author of several books, including Acid Dreams, a social history of LSD.

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poisoning. From a medical perspective, that would be malpractice.

Enhancing Endocannabinoid Tone

Researchers focusing on alcoholism are currently exploring the possibility of "enhancing endocannabinoid tone" by manipulating the enzymes that control 2-AG and anandamide metabolism. One approach relies on URB-597, an experimental drug that inhibits fatty acid amide hydrolase (FAAH), an enzyme that breaks down endocannabinoids. Forestalling the enzymatic degradation of 2-AG and anandamide raises endogenous cannabinoid levels in the brain. FAAH-inhibitors indirectly bolster CB1 receptor signaling.

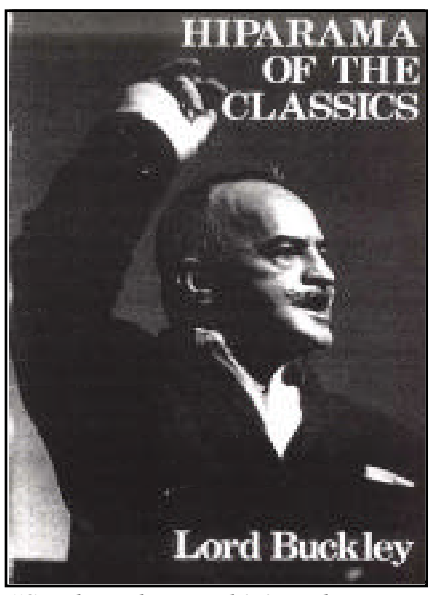
Parsons's rat-brain-microdialysis research suggests that FAAH-inhibitors, by facilitating increased CB1 activity, can reduce anxiety-like behavior associated with alcohol dependence. FAAH inhibitors have also demonstrated therapeutic benefit in animal models of other severe disorders, including neuropathic pain, neural degenerative conditions, epileptic seizures, hypertension, depression, and inflammatory bowel disease, as well as against the proliferation and migration of cancer cells, according to Stephan Petrosino and Vincenzo Di Marzo at the University of Naples.[8]

Additional studies indicate that genetic mutations may contribute to the dysregulation of endocannabinoid signaling. Scientists have linked a predilection for excessive alcohol intake to "polymorphisms" (atypical amino acid sequence repeats) in FAAH and CB1 receptor genes. A naturally-occurring "single nucleotide polymorphism" in the gene encoding the endocannabinoid inactivating enzyme FAAH is often found in people who engage in problem alcohol and drug use. This same FAAH gene polymorphism, according to German researchers, is often present in patients with obesity and irritable bowel disease.[9]

Of course, there is another way to enhance CB1 signaling and adjust enzymatic processes —one could smoke, vaporize or eat cannabis, a natural, nontoxic herb, and thereby influence gene expression. THC, as noted earlier, activates both the CB1 and CB-2 receptors. And CBD, the second most prominent cannabinoid in marijuana, inhibits FAAH! What's more, THC and CBD work best in tandem, synergistically, so to speak, along with dozens of other phytocannabinoids, terpenes and flavonoids that are found in cannabis.

Endocannabinoid deficiency?

If alcoholism is an endocannabinoid deficiency syndrome, then it makes perfect sense that people might successfully



"Smoke a thousand joints, but never open up the bottle. No one ever won the war against John Barleycorn."
—Lord Buckley

Many references in the medical literature support the use of marijuana in the treatment of drug and alcohol addiction.

wean themselves from booze by smoking marijuana, which triggers cannabinoid receptor signaling. In 1891, Dr. J.B. Mattison, writing in the *St. Louis Medical and Surgical Journal,* described cannabis as a "remarkable" treatment for drug and alcohol dependence. Many references in subsequent medical literature support the use of marijuana in the treatment of drug and alcohol addiction.

There is compelling evidence that alcohol consumption diminishes among those who "self-medicate" with cannabis. A NIDA-funded investigation in Jamaica in the mid-1970s concluded that ganja smokers drank much less alcohol than non-smokers, lending credence to the notion that widespread marijuana use was the main reason for significantly lower levels of alcoholism in Jamaica than anywhere else in the Caribbean.[10]

Other surveys have shown that a reduction in marijuana use leads to increased alcohol consumption among the stressed-out masses. After medical marijuana was legalized in California in 1996, Dr. Tod Mikuriya and several like-minded physicians successfully treated hundreds of alcoholic patients who got their lives back after switching to pot.

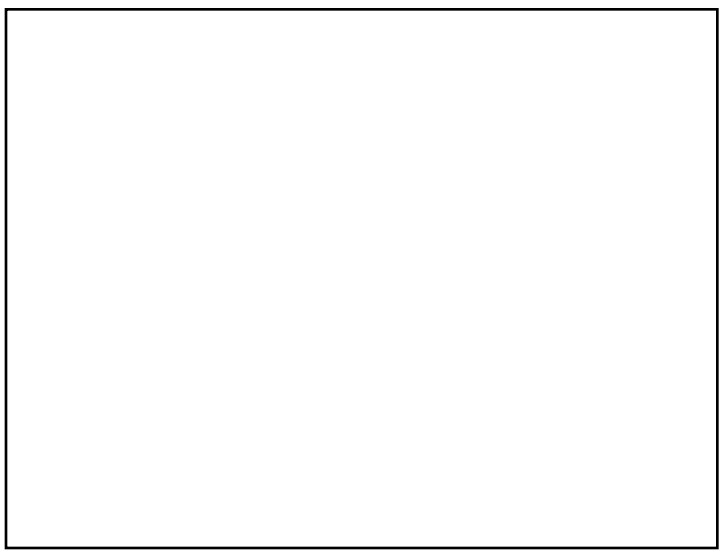
Parsons' brain research implicitly validates cannabis substitution as a harm reduction strategy for treating alcoholism. But the idea of substituting marijuana for alcohol and other addictive substances is still strictly taboo in NIDA-contracted scientific laboratories, where synthetic enzyme-tweakers are favored over the "kind bud."

FAAH-inhibitors are still years away from FDA approval. For those who are unable or disinclined to stop using psychoactive substances completely, marijuana may provide a safe and effective alternative to Alcoholics Anonymous, which emphasizes complete abstinence.

To assess the extent to which medical marijuana patients are using the herb as a replacement for alcohol and/or prescription pharmaceuticals, Amanda Reiman, a lecturer at the University of California's School of Social Welfare in Berkeley, surveyed 350 members of the Berkeley Patients Group (BPG), a city-licensed medical marijuana dispensary. Reiman, BPG's research director, presented her findings at the 2009 ICRS conference, which was attended by a BPG activist contingent. Forty percent of respondents said they used marijuana as a substitute for alcohol.

"When addressing the efficacy of cannabis as a substitute for alcohol, all participants reported cannabis substitution as very effective or effective," Reiman noted. Twenty-six percent of those surveyed said they used marijuana to replace more dangerous illegal drugs. Fifty-seven percent asserted that marijuana provided better relief for their symptoms than conventional medications, and 66 percent said they used cannabis as a replacement for prescription pills.[11]

Rather than being a so-called gateway to hard drugs and addiction, marijuana is an exit drug for many self-medicators. Reiman and others have found that cannabis enables people to minimize or eliminate their use of more harmful substances, including prescription meds, opioids, and alcohol.



Fellowship of 12-step programs is useful to addicts and alcoholics in recovery. But those who use cannabis to reduce the craving for alcohol and/or hard drugs must practice less than rigorous honesty if they attend meetings. Some cannabis dispensaries now sponsor recovery-oriented support groups.

"The fact that alcohol causes so many problems in our society is not a reason to keep pot illegal; rather it is the reason we must make it legal," assert the authors of *Marijuana is SAFER —so why are we driving people to drink?*

Paul Armentano, Steve Fox and Mason Tvert are veteran reform advocates who have honed their arguments against pot prohibition and the legal double standards that privilege wine over weed. Now they have compiled them in a *J'Accuse*-like manifesto. The bottom line: if legalizing marijuana results in a decline in alcohol use, that's a good thing from a public health perspective.

And if it results in the wider use of marijuana, with its demonstrable neuroprotective properties, so much the better.

References

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