COMMENTARY

A Discount on Cannabinoids

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Signs posted in coffee shops throughout California warn their readers that "chemicals known to cause cancer and reproductive toxicity are present in coffee, baked goods and other foods or beverages sold here." Undeterred by the admonition, every day millions of Californians eat their morning muffin accompanied by a hefty coffee drink. Why does the warning go unheeded? Because, like all humans, the health-minded citizens of the Golden State tend to discount the value of delayed risks by a factor that increases with the length of the delay. The danger posed by carcinogens is not an immediate one and can be dismissed because it lies somewhere in an undefined future. Something similar happens, as it turns out, with rewards. When people are asked whether they would prefer a small reward today or a larger reward tomorrow, a sizable fraction of responders pick the lesser and quicker option; but if the choice is between a small reward in 1 year and a larger reward in 1 year plus 1 day, almost no one takes the first alternative. Somehow, after a long wait, holding back for 1 extra day stops being a problem. This time inconsistency is due to an effect economists call hyperbolic discounting, an unconscious bias in favor of the present that pushes humans (and other animals) to choose smaller sooner rewards over larger later ones. This makes good adaptive sense—after all, saving a treat for tomorrow is not always a smart strategy if you live in a world full of danger. Nevertheless, when brought to excess, hyperbolic discounting can lead people astray. This can happen, for example, when normal individuals make hasty decisions or take risky actions without thinking about their future consequences. But it also happens with particularly high frequency in substance abuse and other disorders in which impulsivity plays a considerable role (1). Recent studies in animal models, including an article published in the current issue of *Biological Psychiatry* (2), suggest that endogenous cannabinoid neurotransmission is an important regulator of the neural mechanisms that discount future gains in favor of immediate ones.

The endocannabinoids are lipid-derived neurotransmitters that activate cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 receptors—the same G protein-coupled receptors targeted by Δ^9-tetrahydrocannabinol in marijuana [for review, see (3)]. As one of the most recent entries in pharmacology textbooks, these substances are still only partially understood. Most researchers agree, however, that they operate in a radically different way from traditional neurotransmitters, in that they are generated on demand through enzymatic cleavage of membrane-bound phospholipid precursors rather than being released by calcium-driven vesicle secretion. Two endocannabinoids have been identified with reasonable certainty: anandamide and 2-arachidonoyl-sn-glycerol (2-AG). Both molecules are chemically related to arachidonic acid—in anandamide, this polyunsaturated fatty acid forms an amide with ethanolamine, while in 2-AG it binds glycerol through an ester bond. In the brain and elsewhere in the body, anandamide and 2-AG act as paracrine messengers, diffusing over relatively short distances from their site of production to activate receptors on the surface of neighboring cells. The spatially restricted nature of these actions, along with the predominantly presynaptic localization of CB_1 receptors in the brain, have led to suggest that the main synaptic function of the endocannabinoid system may be to convey retrograde signals that bridge activated dendritic spines to the axon terminals impinging upon them (3). Excitatory synapses in the nucleus accumbens (Acb), medial prefrontal cortex, and other regions of the brain provide one of the best understood illustrations of this signaling process. In dendritic spines of these synapses, type-5 metabotropic glutamate receptors are part of a multi-protein complex that also contains phospholipase C-β and diacylglycerol lipase-α, two enzymes needed to release 2-AG from its precursor molecule (3). When glutamate binds to type-5 metabotropic glutamate receptors, the physical vicinity of this receptor to phospholipase C-β and diacylglycerol lipase-α enables a quick and localized spike in 2-AG production. The newly formed messenger escapes the spine and crosses the synaptic cleft to engage presynaptic CB_1 receptors, with the primary end result of reducing calcium channel activity and inhibiting glutamate release (3) (Figure 1).

Endocannabinoid-mediated retrograde signaling modulates synaptic function in many regions of the brain, including the basolateral nucleus of the amygdala (BLA) and the Acb—two structures that are also deeply involved in regulating impulsivity. In neurons of the BLA, for example, anandamide mediates long-term depression of gamma-aminobutyric acidergic inhibitory transmission (4), while in the Acb, 2-AG is responsible for a distinct type of long-term depression at glutamatergic excitatory synapses (5). Cardinal *et al.* (6) and Winstanley *et al.* (7) have conclusively shown that selective lesions of either of these two brain regions render rats more inclined to choose smaller sooner rewards over larger later ones. These investigators used a delayed-discounting task in which food-restricted rats were given the choice between two levers: one delivered a small reward (one sugar pellet) immediately, while the other delivered a large reward (four pellets) after a time lag that increased progressively during each experimental session. For short delays, rats trained on this task preferred the larger later pay off, but extending the wait increased the animals' preference for the smaller sooner option. Damage to the BLA or the core subregion of the Acb—but not to the anterior cingulate, medial prefrontal, or orbitofrontal cortices—produced a persistent deficit in the rats' ability to postpone gratification (6,7). Importantly, a similar tendency to perform impulsively was seen in rats trained to self-administer cocaine and then tested in the same delayed-discounting task (8).

With this information in hand, Hernandez *et al.* (2) set out to determine whether endocannabinoid signaling might regulate impulsivity in rats sensitized to cocaine. After having confirmed that repeated injections of this psychostimulant impaired

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Received Jan 21, 2014; accepted Jan 22, 2014.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2014.01.010

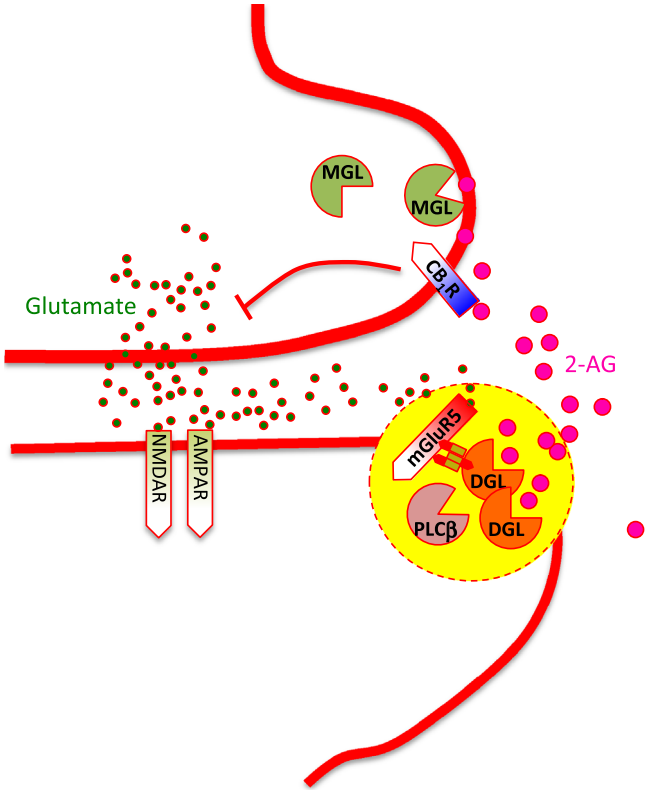

Figure 1. 2-Arachidonoyl-sn-glycerol (2-AG)-mediated endocannabinoid signaling at excitatory synapses of the brain. A multi-protein complex found in the perisynaptic region of the dendritic spine joins in a single functional unit three key proteins needed for 2-AG production—type-5 metabotropic glutamate receptors (mGluR5), phospholipase C-β (PLC-β), and diacylglycerol lipase-α (DGL-α). The physical proximity of mGluR5 to PLC-β and DGL-α allows for a rapid increase in the local levels of 2-AG, which diffuses across the synaptic cleft to activate cannabinoid receptor type 1 (CB_1) cannabinoid receptors (CB_1R) on axon terminals and modulate glutamate release. The biological actions of 2-AG are terminated, within nerve terminals, through enzymatic hydrolysis catalyzed by monoacylglycerol lipase (MGL). AMPAR, alpha-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; NMDAR, *N*-methyl-D-aspartate receptors.

self-control in the behavioral task described above, the researchers found that administration of a CB_1 receptor antagonist counteracted cocaine-induced impulsivity—both preventing its development and reversing it after its establishment. Importantly, CB_1 blockade influenced task performance only in rats sensitized to cocaine, not in rats treated with vehicle, suggesting that endocannabinoid activity may specifically contribute to the loss of self-control associated with cocaine sensitization. What neural adaptations might bring about this effect? Hernandez *et al.* (2) did not answer this question, but ran another experiment which implied that changes in dopamine transmission could be important.

Dopamine neurons in the ventral tegmental area of the midbrain are involved in reinforcement learning and in guiding decisions about reward; for example, they fire more strongly when rats are presented with cues that predict the larger or more immediate of two possible reward outcomes (9). These neurons project extensively to the forebrain and their electrical activity causes discrete (phasic) rises in synaptic dopamine levels within the Acb, which can be measured by fast-scan cyclic voltammetry (a technique that allows to quantify extracellular concentrations of electrically responsive molecules such as dopamine with a temporal resolution on a subsecond time scale). Hernandez *et al.* (2) utilized this approach in rats that were performing a delayed-discounting task. The researchers found that dopamine release in the Acb was stronger for the large reward option when the delay to obtain the reward was minimal but became stronger for the small reward option when the large reward was postponed. Exposure to cocaine reversed this pattern, such that dopamine release always increased for the small reward choice at minimal or moderate delays. Finally, administration of a CB_1 receptor antagonist normalized phasic dopamine release in cocaine-treated rats, making it indistinguishable from that seen in naïve animals. These results nicely match the behavioral data suggesting, as the authors of the study conclude, that the endocannabinoids play an obligatory role in the development of cocaine-induced impulsivity and its neurochemical correlates.

The study raises a number of interesting theoretical questions. Most intriguing among them is arguably the identity of the endocannabinoid transmitter involved in regulating impulsive choice. Since the functions of anandamide and 2-AG in the brain appear to be distinct and nonoverlapping (10), it will be essential to determine which of the two substances is responsible for facilitating the loss of self-control induced by cocaine. It will also be important to define the brain localization of this regulatory process: Hernandez *et al.* (2) convincingly argue for (but do not prove) a role of the ventral tegmental area and the Acb, but this does not exclude the contribution of other regions such as the medial prefrontal cortex and the BLA. In addition to stimulating new experiments, the study also opens the exciting therapeutic perspective of utilizing CB_1 receptor antagonists, alone or in combination with behavioral interventions, to enhance self-control in persons addicted to cocaine. If confirmed by clinical data, this would be a truly significant indication for a class of drugs that does not yet have a role in therapy.

The author is founding director of the unit of Drug Discovery and Development at the Italian Institute of Technology (Italy). He is also scientific cofounder of and consultant for Thesan Pharmaceuticals, Inc., and iMetabolite Inc., in which he retains equity interest. He is an inventor on issued patents and patent applications, assigned to the Regents of the University of California, that disclose pharmacological modulators of signaling mediated by endocannabinoids and other lipid mediators. *His laboratory is currently funded by the National Institute on Drug Abuse, the National Institute of Diabetes and Digestive and Kidney Diseases, the Asthma Foundation, and Thesan Pharmaceuticals.*

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