The role of the endocannabinoid system in addictive behavior

The revolution on cannabinoid research started when the primary psychoactive constituents of cannabis, Δ⁹-THC and Δ⁸-THC, were isolated in 1964 (Guoni & Mechoulam 1964). This finding triggered the identification (Devane et al. 1988; Herkenham et al. 1991) and cloning (Matsuda et al. 1990) of its cellular target, the cannabino-
id receptor (CB₁), and a second mainly peripheral
CB₂ receptor (Munro, Thomas & Abu-Shaar 1993).

The next cornerstone in cannabinoid research was the identification of natural ligands for the CB₁ receptor: arachidonylethanolamide, named anandamide from the Sanskrit 'internal bliss' (Devane et al. 1992), and 2-arachidonoylglycerol (Mechoulam et al. 1995; Sugitaa et al. 1995). The complete picture of the endocannabinoid system (ECS) was achieved with the description of a bio-
chemical pathway for its synthesis, release (Di Marzo et al. 1994; Cadas et al. 1996), transport (Beltramo et al. 1997) and degradation (Cravatt et al. 1996) of the endocannabinoids.

The relevance of this system in the organism is extensive and involves not only the central nervous system, affecting memory, cognitive and mood processes, but also the autonomic, immune and reproductive system, the endocrine network and the gastrointestinal tract (Di Marzo et al. 1998). The importance of the ECS is further reflected in its conservation across the evolution. It is estimated that the ECS evolved in primitive animals over 500
million years ago (McPartland et al. 2006).

A recent and growing body of evidence indicates a role of the ECS in different states of the addiction process, ranging from the acquisition and maintenance of drug-taking behaviors to craving and relapse. Here I will comment on the most recent publications in Addiction Biology related to the ECS [published in issue 18(6); see also publication trends Helsinki and Spanagel, 2011] and evaluate their relevance and contribution to the knowledge about cannabinoid research in both human and animal studies.

Human research on the ECS has focused primarily on
the modulation of cognitive and emotional processes after acute or chronic cannabino
d treatment, and on the link between cannabis use and the development of psychosis-related disorders. Another extensively studied topic is the heritability of cannabis abuse and the identification of genetic variants of the ECS associated with addiction.

Neuro-imaging studies in the context of reward-related processes and cannabinoids are very limited, but two studies published in 2012 have provided interesting novel data. In the first study, using functional magnetic resonance imaging, Cousijn et al. (2013) investigated potential differences in brain activity between healthy and cannabis user subjects during a decision-making task. The authors found that higher brain activity during an immediate reward predicts increased cannabis use. This study reveals a potential new vulnerability marker (or endophenotype) for the development of a substance use disorder (SUD). At this point, a study by Euser et al. (2013) should be mentioned, in which electroencephalogram recordings were analyzed during an error-processing task in 32 high-risk adolescents with at least one parent under SUD treatment. The authors found that these adolescents showed diminished error-processing abilities and were characterized as using cannabis more frequently, supporting the conclusion made by Cousijn and collaborators. The second neuro-imaging study (Leroy et al. 2012) examined the activity of the dopamine transporter (DAT) in healthy, tobacco-dependent and cannabis-dependent smokers. The authors found a widespread decrease in cerebral DAT availability in both tobacco and cannabis smokers compared with non-smokers. This is the first reported in vivo data set measuring DAT in cannabis smokers, and a major finding of this study is that the reduction in DAT was not only observed in striatal areas, but involved all dopaminergic pathways.

The question of cannabis abuse heritability is repre-
sented by two recent genetic studies in Addiction Biology. In the first genetic study, Agrawal et al. (2011) reported the first genome-wide association study (GWAS) of can-
abis dependence, conducting an association analysis between almost 950 000 genetic variants and lifetime DSM-IV cannabis dependence with 708 cannabis-dependent and more than 2000 control subjects. Surprisingly, none of the association signals explored in the study reached genome-wide significance, and the authors concluded that both replication and meta-analysis are required to confirm the results. Indeed, the second study (Verweij et al. 2012) did so, and performed a GWAS for replication of 10 previously identified candidate genes for cannabis use in 7452 families from the Australian Twin Registry. Their findings demonstrate that none of the 10 candidate genes are associated with lifetime cannabis use. Although the authors recognized a potential limitation of the study by trying to associate the phenotype of cannabis use with some genes that were
previously associated with late stages of addiction, this issue may be counteracted by the much larger number of subjects tested in comparison to other studies.

In a recent meta-analysis published on published reports on genetic variants of the CB1 receptor gene (CNR1) in SUDs (Benyamina et al. 2011), one polymorphism (the AAT) showed significant association with substance dependence in the Caucasian population samples. The authors concluded that the CNR1 AAT polymorphism has a minor impact on illicit substance dependence vulnerability, a finding that may result from the wide heterogeneity between the studies. However, this minor association may also reflect the complex role of the ECS in addictive behavior. This complexity becomes even more evident at the therapeutic level, as reflected by the few (primarily behavioral) available treatments for cannabis dependence; only recently a number of studies are trying to identify potential pharmacotherapies (for reviews, see Vandrey & Haney 2009; Sturgess et al. 2011). A recent study published by Cooper et al. (2013) shows that quetiapine, an atypical antipsychotic, is able to improve some of the symptoms associated with marijuana withdrawal, such as sleep quality, decreased caloric intake and body weight loss. However, this drug also increases marijuana craving and relapse. Obviously, the authors excluded quetiapine as a potential therapy for marijuana dependence.

The contribution from animal studies is extremely important for a better understanding of the ECS, for one obvious reason: they allow us to perform experiments for which the clinical field is practically and ethically limited. One main research topic focuses on early exposure to cannabinoids and its long-lasting effects. As early as 1970s, it was demonstrated that rats exposed daily to marijuana exhibited motor and learning alterations 2 months following administration (Fehr, Kalant & LeBlanc 1976), and over the last decades, there has been solid evidence demonstrating that early cannabinoid exposure results in multiple long-lasting cognitive and affective alterations and vulnerability to addiction (Schneider 2008). Two novel publications have now complemented and extended the knowledge on that research topic, demonstrating how early ECS stimulation increases the vulnerability for certain psychiatric disorders like SUDs in a sex-dependent manner. The first (Winsauer et al. 2011) examined, in female rats, whether ovarian hormones would attenuate the long-lasting effects of a periadolescent cannabinoid treatment. The authors found that early chronic drug administration not only impaired learning processes but also produced alterations in the function and density of striatal and hippocampal CB1 receptors in adulthood, alterations dependent on the ovarian hormones. In the other study by Lorente-Berzal et al. (2011), it was reported that adolescent cannabinoid exposure also resulted in long-term cognitive and emotional alterations in a sex-dependent manner, as females were more affected. In males, cannabinoid treatment did not affect anxiety-related behavior, but the endocrine response to stress, as measured by hypothalamic-pituitary-adrenal axis responsiveness, was increased. In contrast, the phenotype in females was characterized by a higher novelty-seeking behavior and decreased attentional ability, two core traits that have been shown to increase vulnerability to drugs of abuse.

Noteworthy, the involvement of the ECS on the vulnerability to develop addiction is not exclusively dependent on its manipulation during adolescence. Inmates differences in the ECS have been extensively explored in the context of alcohol research (for a review, see Bilbao 2013) using genetically modified or selected animal models. A recent study by Vinod et al. (2012) adds a relevant piece of information, showing that compared with the selectively bred non-alcohol-prefering rat line, the Sardinian alcohol-prefering rats express an innate altered ECS. In summary, these findings support the idea that an innate altered ECS is a potential genetic basis leading to high alcohol drinking.

Another focus of interest on the ECS in animal research is identification of the anatomical targets mediating the reinforcing effects of cannabinoids. This issue is not trivial due to the complexity of the ECS in the brain, with widespread expression of CB1 receptors and their multiple interactions with other neurotransmitter systems. A good example of this line of research is provided by a preclinical study performed by Justinová et al. (2011) using squirrel monkeys and rats. In this study, the authors combined behavioral, pharmacological and biochemical approaches to investigate the specific interactions between the endocannabinoid and adenosine systems in the context of cannabinoid reinforcement. They showed that A2A receptors selectively modulate cannabinoid-induced reinforcement and dopamine release, as the A2A antagonist did not affect these responses under cocaine or food self-administration. Furthermore, this modulatory role of A2A receptors on cannabinoid reinforcement is restricted and does not cover the different phases of the addiction cycle, as illustrated by the fact that pharmacological manipulation of A2A receptors failed to affect reinstatement of THC-seeking behavior.

In another study, Crundel et al. (2013) explored the interactions of the ECS with the mesolimbic dopaminergic reward system using positron emission tomography. In rats treated chronically with the CB1 antagonist rimonabant (SR141716A), the authors observed increased dopamine D2 receptor availability in the dorsal striatum, and in the ventral striatum using higher doses of the drug, which was accompanied by an increase in
body weight. This simple but relevant study clearly shows
the involvement of the ECS in reward-related processes.

The interaction of the ECS with nicotine reinforcement
has also been assessed. Simonnet, Cador & Caille
(2013) demonstrated for the first time that pharmacological
blockade of the CB1 receptors in the ventral tegmental
area (but not in the nucleus accumbens) has an inhibitory effect on intravenous nicotine self-
administration in rats. These findings are complemented
by a study using pharmacological stimulation of the CB1
receptor showing increases not only in nicotine intrave-
nous self-administration but also in reinstatement of
nicotine-seeking induced by the presentation of nicotine-
associated contextual cues (Gamaleldin et al. 2012).

Méndez-Díaz et al. (2012) demonstrated that the
hedonic value of food was increased when rats were given
cannabinoids, and was decreased when rats were admin-
istered a CB1 antagonist. Using a food-conditioned place
preference paradigm, they observed that central stimula-
tion or blockade of the ECS induced an increase or a
decrease, respectively, in the time spent in a compartment
previously associated with food availability. The authors
concluded that the ECS may be involved in the rewarding
experience and subjective sensation of food palatability.

If this is the case, then the question arises: do the ECS
represent a common substrate mediating the reinforcing
properties of drug and natural rewards? There is no study
that has addressed this question explicitly, but the last
study that I will comment on may support this idea. Le
Merrer et al. (2012) identified a common transcriptional
pattern of regulation of several genes in the extended
amygdala following the presentation of different rewards.
Interestingly, the CB1 receptor gene was included, and
most genes belonged to a common network—the
hunntnin—not previously described in addiction
research. They concluded that abstinence from drugs of
abuse involves a common gene network.

CONCLUSION

The studies included here support the critical role of
the ECS in reward-related processes. Given the wide range
of actions on reinforcement processes and mechanisms
relevant to addictive behavior, one important question
remains to be answered: Does the ECS represent a common
substrate for the primary and secondary reinforcing prop-
erties of drugs of abuse and natural rewards?

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