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GUEST EDITORIAL

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The endogenous cannabinoid system and drug addiction: 20 years after the discovery of the CB1 receptor

Cannabis sativa preparations (hashish, marijuana) have been used by humans for the last 5000 years. But being one of the oldest recreational drugs with abuse potential, its neurobiological mechanisms remained obscure until the isolation and identification in 1964 of Δ^9tetrahydrocannabinol (THC), its main psychoactive constituent, by the group of Ralph Mechoulam (Gaoni & Mechoulam 1964). THC was the first of a series of a new class of drugs termed cannabinoids, but despite this finding, the brain targets of THC remained unidentified for another long period. It was in November 1988, 20 years ago, when a seminal paper by the group of Allyn Howlet (Devane *et al.* 1988) identified pharmacologically the presence in the brain of a G protein-coupled receptor as the target of natural cannabinoids. It was followed immediately by the molecular cloning of the cannabinoid receptor (Matsuda *et al.* 1990) and by the identification by the group of Raphael Mechoulam of the first endogenous ligand of the cannabinoid receptor, an arachidonic acid derivative termed anandamide (Devane *et al.* 1992). This discovery completely changed the research on cannabinoids and marijuana and led to one of the most active fields of research in neuropharmacology. As an example, 2924 cannabis-related papers were published until 1988. From 1988 to-date, 7183 scientific communications can be found in biomedical databases. In 20 years, the *cannabinoid* field has generated three times more documents than in the whole anterior period. Table 1 summarizes the most important hints on cannabinoid research since the discovery of the first cannabinoid receptor.

Why is the discovery of the cannabinoid receptor so important? And why a special issue in *Addiction Biology*? The identification of a specific receptor for THC opened not only the gate to an active research on the neurobiology of cannabis abuse, it also allowed the scientific community to identify an evolution-preserved, widely distributed modulatory system that participates in multiple physiological processes such as motivated behaviours, emotional homeostasis, memory storage or motor control (Fig. 1). In fact, the potentiality of the endogenous cannabinoid system as a target for the development of new medicines can be envisioned by simply paying attention to the multiple inventions surrounding its discovery. Table 2 shows the patents filed in the last 15 years, most of them by major pharmaceutical companies, protecting the utility of methods and compounds related to the endogenous cannabinoid system for applications on multiple disorders. Few fields on science can show such an explosion of technology. We can expect a reasonable pay-off from these patents in the next 10 years. In fact, a first medicine based on the cannabinoid CB1 receptor, the antagonist rimonabant, is already in the market for complicated obesity, and many others are already on clinical trials.

Regarding addiction, many different approaches identified how natural cannabinoids modulated reward systems and induced tolerance. But only with the identification of the cannabinoid CB1 receptor did we come to understand why cannabinoids did so and how the endocannabinoid system participated in cannabis addiction (Table 1). Research has demonstrated how animals self-administer cannabinoid CB1 receptor agonists and how cannabinoid receptor antagonist suppresses cannabinoid-induced positive reinforcement. Moreover, cannabinoid withdrawal in animal models and in humans was identified and explained on the basis of the presence of the CB1 receptor in specific brain circuits. But the real surprise came from the discovery of the role of the endogenous cannabinoid system in general reward process and in the neurobiology of addiction. Both the endocannabinoids and the cannabinoid receptor appear to be crucial in opioid, alcohol, psychostimulant and nicotine addiction. Its presence in reward circuits allows a clear modulation not only of reward, but also of relapse processes, a key issue on drug abuse therapy. This is the justification for the present issue on cannabinoids in *Addiction Biology*. The intense work developed for the past 20 years by researchers throughout the world has placed the CB1 receptor and the endogenous cannabinoid system in the center of the search for new therapies on addiction. This issue also wants to pay homage to the seminal work of those who devoted their scientific career to this field, specially to Dr. Miguel Navarro, who passed away recently. His essential contribution to the understanding of opioid–cannabinoid interactions, to the role of endocannabinoids on alcoholism and to the cannabinoid CB1 receptor modulation of anxiety merits our recognition.

We have put together a wide overview of the endogenous cannabinoid system on addiction. The first article of the invited reviews, by Roger Pertwee, gives a detailed

Table 1 Chronology of selected discoveries on the feld of cannabinoids. The identification of the cannabinoid receptor in 1988 and anandamide in 1992 marked the initiation of a tide of research findings that led to the discovery of the endogenous cannabinoid system and to the first clinical application of an endocannbinoid-based therapy in less than 20 years.

Year	*Discovery*	*Citation*
1964	Identification of the chemical structure of Δ^9-tetrahydrocannabinol	Gaoni & Mechoulam (1964)
1984	First proof that cannabinoids decrease cyclic adenosine monophosphate, suggesting mediation by a Gi/o-coupled receptor	Howlett & Fleming (1984)
1988	Identification of the CB1 receptor	Devane *et al.* (1988)
1990	Molecular cloning and mapping of CB1	Herkenham *et al.* (1990); Matsuda *et al.* (1990)
1992	Identification of the first endogenous ligand on CB receptors: arachidonyl ethanolamine (anandamide, AEA)	Devane *et al.* (1992)
1993	Identification of the CB2 receptor	Munro, Thomas & Abu-Shaar (1993)
1994	Development of SR141716A (rimonabant)	Rinaldi-Carmona *et al.* (1994)
1994	Mechanisms of cannabinoid biosynthesis	Di Marzo *et al.* (1994)
1995	2-arachidonoyl glycerol, a second endocannabinoid	Mechoulam *et al.* (1995); Sugiura *et al.* (1995)
1996	Fatty acid amidohydrolase, the first enzyme degradating endocannabinoids	Cravatt *et al.* (1996)
1997	Evidence for anandamide transport	Beltramo *et al.* (1997)
1997	Neurobiology of cannabinoid dependence and withdrawal	Rodriguez de Fonseca *et al.* (1997)
1999	Generation of CB1-receptor knockout mice	Ledent *et al.* (1999)
2001	Functional role for CB1 receptors in drug self-administration and relapse	De Vries *et al.* (2001); Navarro *et al.* (2001)
2001	First demonstration that endocannabinoids modulate synaptic transmission in the brain	Kreitzer & Regehr (2001); Ohno-Shosaku, Maejima & Kano (2001); Wilson & Nicol (2001)
2001	First evidence for the existence of further cannabinoid receptors	Hájos, Ledent & Freund (2001)
2002	Endocannabinoids mediate extinction of aversive memories	Marsicano *et al.*
2003	Anandamide degradation and anxiety	Kathuria *et al.* (2003)
2005	First clinical indication for cannabinoid CB1 receptor antagonists	Van Gaal *et al.* (2005)

Table 2 Cannabinoid technology: patents registered on international databases claiming potential utility for human health of endocannabinoid system-acting compounds. Part of these claimings includes addiction therapy. As an example, 21 out of 142 patents on cannabinoid receptor antagonists include the potential utility for the treatment of drug abuse.

Target (receptor, enzyme)	*Number of patents*
Cannabinoid receptor antagonists	142
Cannabinoid receptor agonists	130
Vanilloid receptor VR1 ligands	49
Inhibitors of fatty acid amidohydrolase	27
Inhibitors of diacylglicerol lipase	4
Inhibitors of monoacyl glicerol lipase	4
Inhibitors of anandamide transport	5
Ligands for GPR55 receptors	2
Total	363

summary of ligands binding to the CB1 receptor in the brain. Jose A. Lopez-Moreno *et al.* are presenting an overview on the pharmacology of the endocannabinoid system in relation to behavioural addiction. The latest findings on the reinforcing properties of cannabinoids and cannabis dependence—a topic that has been up for debate for a long time—will be presented by Ziva Cooper and Meg Haney. When it comes to addiction, both emotional behaviour and learning processes stand as major factors contributing not only to the development but also to the retention of addictive behaviour. These important factors in the context of addiction are reviewed by Fabricio Moreira and Beat Lutz. Furthermore, reviews about the interaction between the endocannabinoid system and other drugs of abuse and related neurotransmitter systems are presented. The review by Patricia Robledo *et al.* is reporting on the scientific advances on cannabinoid–opioid interaction. The role of the CB1 receptor in psychostimulant addiction is discussed by Joost Wiskerke *et al.* Le Foll *et al.* present a review on CB1 blockade as a useful treatment of nicotine dependence. In fact, cannabinoid CB1 receptor blockade has undergone clinical trials for its efficacy on tobacco smoking cessation.

Besides the importance of the endogenous cannabinoid system on neurobiological processes related to addiction, we could not skip to review the impact of cannabis exposure on health, focusing on addiction and psychiatric disorders. Growing evidence suggest that

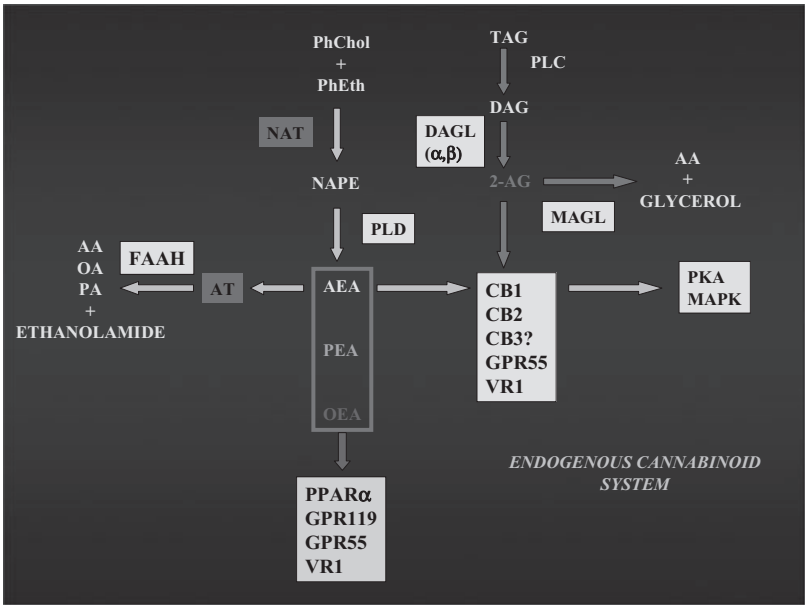

Figure 1 A summary of the endogenous cannabinoid system. The two main endocannabinoids are anandamide (AEA) and 2-arachidonoylglicerol (2-AG). They act mainly through cannabinoid CB1 and CB2 receptors, although additional targets include the vanilloid VR1 receptor, the GPR55 orphan receptor and a yet-to-be-cloned CB3 receptor identified in the hippocampus. The parents acylethanolamides, palmithylethanolamide (PEA) and oleoylethanolamide (OEA), act through different receptor systems [the orphan receptor GPR119 and the peroxisome proliferator activated-receptor alpha (PPARα)]. While AEA is produced by the ezyme NAPE-PLD, which cleaves the membrane phospholipid NAPE (synthesized by a yet-to-be-cloned enzyme NAT), 2-AG is produced by the metabolism of diacylglicerol through the actions of specific diacylglicerol lipases (DAGL). Both AEA and 2-AG are incorporated by a transporter (AT) into cells. AEA, PEA and OEA are degraded by the enzyme fatty acid amidohydrolase (FAAH) to ethanolamine plus arachidonic (AA), oleic (OA) or palmitic (PA) acids. 2-AG is degraded by a monoacylglicerol lipase (MAGL).

puberty might represent a specific vulnerable period for the adverse consequences of cannabinoid exposure. This issue is reviewed by Miriam Schneider. Finally, the article by Dagmar Koethe and Markus Leweke describes the role of cannabis in psychiatric disorders beyond addiction.

As editors of this special issue, we wish to thank the enthusiastic support of all the contributors. We would like to express our gratitude to all the reviewers who made it possible to assure the excellent quality of the articles included herewith. We specially thank the Editorial Office of *Addiction Biology* for its continuous support and patience. We are sure that in the next 20 years, the cannabinoid system will pay-off all the expectancy generated. And we will be there to report it.

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