EDITORIAL

Cannabis and Endocannabinoids: 'The Old Man and the Teenagers'

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The title of this *Editorial* requires some explanation. The main idea of this special issue was to cross two timescales. The one from the plant *Cannabis* to the cannabinoid receptors started 5,000 years ago – more than five times *Methuselah*'s lifespan – and the second one began in 1992, just the time of adolescence. I was thinking also that, in a single life, scientists were lucky to read three important pages of cannabinoid science: the isolation and structure elucidation of the major psychoactive ingredient in 1964, the characterization of the cannabinoid receptors during the eighties and their cloning in the early nineties, and the discovery of the endocannabinoids starting in 1992 with anandamide. Three pages among others, but without these three pages, the book remains hard to read. This led me to search in the literature the inspiration for the title of this *Editorial*, and my first thoughts were for the *Ernest Hemingway*'s novel: '*The Old Man and the Sea*'. Of course the *Old Man* is *Cannabis*, a plant crossing the humankind history and most of the civilizations. And the *Sea* is the numerous effects of this plant, featuring advances in the understanding of fundamental mechanisms. But this title was not entirely satisfactory: where is the place of endocannabinoids in the title? So I moved to '*The Old Man and the Teenagers*', because *Teenagers* have, of course, still to learn from the Old Man, who was for 5000 years the witness of the evolution of Science. In contrast, it is never too late to learn, even for the *Old Man*, and the *Teenagers* in these days of intense technological progress may show the way, for example the use of Web and/or internet by the senior is often due to the teaching of their grandchildren. Similarly, the *Teenagers* featuring here the numerous endocannabinoids discovered so far, and others to come, open new perspectives either in the fundamental neurobiology or in the understanding of *Cannabis* and cannabinoids pharmacological and toxicological properties.

To illustrate the exceptional blooming of the research around *Cannabis* and endocannabinoids, three keywords, *i.e.*, *Cannabis*, cannabinoid, and endocannabinoid, have been introduced in two scientific information databases *Web of Science* and *Pubmed*. Albeit not an absolute picture of the dynamism of the research, it puts on the light some indicative features. The *Table* summarizes the result obtained from the two databases in terms of number of entries per decade. Interestingly, it can be seen that, using the word *Cannabis* – the Old Man – a peak has been observed with 3090 entries during the seventies, followed by about a twofold decrease in the two next decades, and

a renewal of interest in the beginning of the third millennium. With two years and half remaining to achieve the decade, the number of entries with '*Cannabis*' almost reaches the result obtained in the seventies. Using these two databases, the term '*cannabinoid*' seems to appear in a contribution of *Razdan* and *Kane* entitled '*Hashish, a novel cannabinoid containing a cyclic peroxide*' published in the *Journal of American Chemical Society* [1]. Albeit this term is somewhat ambiguous, covering everything from the natural constituents present in the plant *Cannabis sativa* to any kind of chemical substances interacting with the cannabinoid receptors, the tendency is to a significant, sustained, and vigorous increase of the papers using this keyword. A similar increase, even more spectacular, is observed with the term '*endocannabinoid*'. The discrepancy between the results obtained in the two databases might be explained by the period and the number of journals covered by the two databases as well as by the search procedure. In *Web of Science*, the word introduced is searched within article titles, keywords, and abstracts. In *Pubmed*, in addition to this search, the use of MeSH terminology provides a consistent way to retrieve information that may use different terminologies for the same concepts and thus may 're-attribute' previous papers to a newly used keyword. To give an example, using the search word '*endocannabinoid*', the first citation given by *Pubmed* is the original paper of *Devane et al.* [2], describing anandamide, albeit the word '*endocannabinoid*' did not appear in the text. In contrast, the first citation in *Web of Science* is the paper by *Randall et al.* [3] on the comparative pharmacology of endothelium-derived hyperpolarizing factor and anandamide in 1998.

Table

Years	Cannabis		Cannabinoid		Endocannabinoid	
	Web of Science	*Pubmed*	*Web of Science*	*Pubmed*	*Web of Science*	*Pubmed*
1940–1949	–	1		–		–
1950–1959	–	40		–		–
1960–1969	–	399	–	3	–	–
1970–1979	–	3090	–	1629	–	–
1980–1989	47[a])	1370	90[a])	1413	0	0
1990–1999	1032	1596	1510	1954	33	352
2000–2007[b])	2834	2969	4091	4287	1226	1828

[a]) The first citation found in *Web of Science* was from December 1986. [b]) This last search was made on June, 1, 2007.

This issue entitled '*Cannabinoids in Nature and Medicine*' fits well in the scope of *Chemistry & Biodiversity*. The first part has been entitled '*The Phytocannabinoids: The Long Journey from the Plant to the Humans*' and will focus on the plant *Cannabis sativa*, its active ingredients, and the discovery of cannabinoid receptors as well as the therapeutic applications of activating, or blocking, the receptors. The first paper '*History of Cannabis and Its Preparations in Saga, Science, and Sobriquet*' by Dr. *Ethan B. Russo* gives an overview on the plant, its medicinal uses, and its preparations. One attractive feature of his paper is the constant link established between the ancient ethnopharmacognosy related to the recent progress in medical and biological sciences. Then, *Taura* and colleagues invite the reader to enter the plant and to follow the

biosynthetic pathways leading to the production of cannabinoids by *Cannabis sativa* in their chapter entitled '*Phytocannabinoids in* Cannabis sativa: *Recent Studies on Biosynthetic Enzymes*'. The two following chapters are devoted to the pharmacological properties of two major phytocannabinoids: Δ^9-tetrahydrocannabinol and cannabidiol. Dr. *Barbara Costa* in her Chapter '*On the Pharmacological Properties of* Δ^9-*Tetrahydrocannabinol*' deeply describes the pharmacological mechanisms involved in the anti-inflammatory, neuroprotective, antitumoral, and analgesic effects of Δ^9-THC. Prof. *Raphael Mechoulam* and colleagues, in the chapter '*Cannabidiol – Recent Advances*', present the latest findings obtained in the understanding of the molecular targets and pharmacological mechanisms mediating the action of cannabidiol. One of the most awaited discovery in the field, *i.e.*, the cannabinoid receptors, is nicely told by Dr. *Ken Mackie* in his contribution entitled '*From Active Ingredients to the Discovery of the Targets: The Cannabinoid Receptors*'. The historical background, the current state of the knowledge of cannabinoid receptors, as well as personal perspectives are presented. Together with Dr. *Stern*, we then describe the wide imagination of medicinal chemists to bring chemical diversity around the Δ^9-tetrahydrocannabinol and Δ^8-tetrahydrocannabinol moieties. This abundant research began as soon as the elucidation of Δ^9-tetrahydrocannabinol structure as the major psychoactive ingredient was achieved, and was, at least for 25 years, poorly biologically-driven. Dr. *Ethan B. Russo* and colleagues at *GW Pharmaceuticals* gave their insights on the *Sativex*® clinical trials '*Cannabis, Pain, and Sleep: Lessons from Therapeutic Clinical Trials of* Sativex®, *a Cannabis-Based Medicine*'. The pharmaceutical company *GW Pharmaceuticals* is being developing pharmaceutical preparations derived from the plant *Cannabis*, the first of which, '*Sativex® Oromucosal Spray*', received an approval with conditions from Health Canada in April 2005 as an adjunctive treatment for the symptomatic relief of neuropathic pain in patients with Multiple Sclerosis. The following chapter by Dr. *Franjo Grotenhermen* deals with the toxicology of *Cannabis* '*The Toxicology of Cannabis and Cannabis Prohibition*'. In the first part of the chapter, acute and chronic side effects have been reviewed, distinguishing the influence of the dose of absorbed cannabis, while the second part deals with the tricky socio-political problem of cannabis prohibition, especially for suffering people. Directly related to toxicology, the chapter by Dr. *Huestis* reviews the '*Human Cannabinoid Pharmacokinetics*'. This paper considers the classical ADME-Tox parameters with a special emphasis on the absorption depending on the routes of absorption as well as on the interpretation of cannabinoid concentrations in biological fluids. Finally, in the chapter '*Blocking the Cannabinoid Receptors: Drug Candidates and Therapeutic Promises*', Dr. *G. Muccioli* reviews the clinical situations such as obesity, dyslipidemia, addictions, inflammation, and allergies – in which blocking the cannabinoid receptors might be beneficial. Following the tracks of rimonabant, the CB_1 antagonist lead compound, many CB_1 receptor antagonists are now in clinical trials.

The second part of the issue is entitled '*The Endocannabinoid System: The Short Journey from Humans to the Plants*' covers, in terms of scientific publications and knowledge, a somewhat reduced timescale. However, as it will be illustrated in different contributions, even if endocannabinoids have been discovered in 1992, there are a lot of evidence that these signaling molecules have been conserved during evolution, as endocannabinoids have been found in mammals, birds, fish, arthropods, and plants.

Prof. *Hanuš*, in the first chapter '*Discovery and Isolation of Anandamide and Other Endocannabinoids*' detailed with some analytical details the isolation and the elucidation of the structure of anandamide. Other endocannabinoids and endocannabinoid congeners have been also included in this review. The biosynthetic pathways leading to the formation of anandamide are reviewed by *Okamoto et al.* in the chapter entitled '*Biosynthetic Pathways of the Endocannabinoid Anandamide*'. The authors deeply investigate the role of *N*-acylphosphatidylethanolamine phospholipase D (NAPE-PLD), but also consider other biosynthetic pathways of anandamide and other *N*-acylethanolamines from the *N*-acylphosphatidylethanolamine precursors.

The metabolism of endocannabinoids received considerable attention in the last ten years. In '*The Multiple Pathways of Endocannabinoid Metabolism: A Zoom Out*', Dr. *Vandevoorde* and I give an introduction to the best characterized so far enzymes involved in the hydrolysis of endocannabinoids. The chapter also raises the question of the existence of additional enzymes as well as on the interaction of endocannabinoids with cyclooxygenases and lipooxygenases. Nowadays, extensive research, carried out both by academia and pharmaceutical companies, is devoted to the endocannabinoid hydrolyzing enzymes. In the chapter '*Fatty Acid Amide Hydrolases: From Characterization to Therapeutics*', Dr. *Labar* and *Michaux* sum up the current knowledge on the most studied hydrolyzing enzyme fatty acid amide hydrolase (called now FAAH-1) and the recently discovered one fatty acid amide hydrolase (called now FAAH-2). Then, the chapter '*Monoglyceride Lipase as an Enzyme Hydrolyzing 2-Arachidonoylglycerol*' by Dr. *Saario* and *Laitinen* provides a nice overview of a known enzyme but identified only five years ago as being involved in the metabolism of the endocannabinoid 2-arachidonoylglycerol. The last focus on the hydrolyzing enzymes is a contribution entitled '*The* N-*Acylethanolamine-Hydrolyzing Acid Amidase (NAAA)*' by Dr. *Tsuboi et al.*, who describe step by step the evidence accumulated by Prof. *Natsuo Ueda*, demonstrating the existence of an acid amidase also involved in endocannabinoids, and related *N*-acylethanolamines metabolism.

The two last chapters open a new area of research. The chapter '*Genetic Polymorphisms of the Endocannabinoid System*' written by Dr. *Norrod* and *Puffenbarger* illustrate the researches exploring the link between the unbalance of the endocannabinoid system found in several diseases or conditions, and the genetic polymorphisms of the genes encoding for the receptors and enzymes of the endocannabinoid system. Finally, Dr. *Kilaru* and colleagues in the chapter '*The* N-*Acylethanolamine-Mediated Regulatory Pathway in Plants*' summarize their investigations in order to understand the 'endocannabinoid' system in the plant physiology, highlighting the importance of these signaling molecules throughout the evolution. Like in animal systems, *N*-acylethanolamines are formed in plants from *N*-acylphosphatidylethanolamines and are hydrolyzed by an amidase to yield ethanolamine and free fatty acids.

It is the time to let you traveling from a plant, *Cannabis sativa*, to another, *Arabidopsis thaliana*, using cannabinoids and endocannabinoids as keywords. It is time to me to thank all the contributors of the issue for their willingness to share their knowledge and for the very good collaboration. I would like to especially thank Dr. *Giulio Muccioli* for carefully sharing with me the considerable work of reviewing process. Finally, I am indebt to *Chemistry & Biodiversity*, and especially to the Editors

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