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Guest Editorial

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THE CANNABIS PLANT has always held a unique position in human social history and medicine. In ancient times it was smoked or eaten to change mood and emotions, as well as to cure a long list of diseases. In certain countries it was used in religious rites. For centuries it was part of the culture in many lands. In Western Europe and in North America, since the early 19^{th} century, it was used as a medicinal agent and a mood promoting substance, but it became widespread only during and after the 1960's, as part of the expression of youth rebellion.

While the chemistry and pharmacology of opium and coca leaves were thoroughly investigated in the 19^{th} and early 20^{th} century, cannabis was not well understood, as the active constituent could not be isolated in a pure form by the techniques then available and its structure was not elucidated. In the 1960's advances in chromatographic techniques made possible the isolation of Δ^9-tetrahydrocannabinol (THC), which was shown to be essentially the only psychoactive constituent. The isolation and synthesis of THC led to its thorough investigation. Over the next few decades we learned a lot about its pharmacology, biochemistry and clinical effects. However, the mechanism of action of THC was unraveled only after the identification of the cannabinoid receptors and the isolation of endogenous cannabinoids.

The discovery of the endocannabinoid system has brought about a thorough investigation of its functions in mammalian physiology. The ubiquity of its presence and actions were quite unexpected: the endocannabinoid system takes part in an enormous number of processes, be they normal or pathological. The list is really impressive: from suckling and appetite [1,2], through memory effects, including extinction [3.4], reproduction [5,6], neuroprotection [7–12], bone formation (I. Bab, unpublished observations), various immune responses (including inflammation) [13,14], pain [15], gastrointestinal effects [17], cancer [18], the cardiovascular system [16,19], etc. etc. The ubiquitous formation and variety of effects of endocannabinoids pose a problem of specificity. Shouldn't we expect that the endocannabinoids, formed for a specific physiological purpose, would cause additional, possibly undesirable effects? Would endocannabinoids formed for neuroprotection affect reproduction, for example? The mammalian body has found an ingenious solution. Endocannabinoid production is localized and endocannabinoids are apparently formed only on demand. Thus, stimulation of endocannabinoid formation in the hypothalamus may not necessarily lead to effects elsewhere. The endocannabinoids, both anandamide and 2-arachidonyl glycerol (2-AG), being hydrophobic molecules, may bind to cell membranes and their presence in the serum is low. They are also rapidly metabolized (anandamide by a fatty acid amide hydrolase, FAAH and 2-AG by an esterase). Hence the enhanced formation of 2-AG on starvation in the hypothalamus may not affect memory extinction in the hippocampus. And the effects on bones will not be associated with effects on reproduction.

One of the major properties of the endocannabinoids seems to be a protective one. We have learned an enormous amount about the ways the mammalian body protects itself from protein attacks, be they viruses, microbes or parasites. Indeed the whole science of immunology is devoted to the study of these effects. However, the mammalian body needs also to protect itself against non-protein damage. We know much less about this type of protection. Apparently the endocannabinoids play a major role. I expect that we shall learn much about the mechanisms employed by these relatively simple compounds to guard not only the nervous system but possibly other systems in the mammalian body [20].

Many cannabinoids actions seem to be biphasic. Thus, at very low concentrations stimulatory effects are generally observed, while at higher concentrations inhibitory ones are noted. It is yet to be shown that this biphasic mode of action has physiological significance. It seems probable that this is indeed so and the biphasic effects represent a regulatory mechanism in various physiological systems. However, very little work has been done on this topic, which may turn out to be of central importance.

The mammalian body has a large number of fatty acids as well as amino acids and amines – most of these natural products, are in some conjugated form. For reasons of biological economics it seems reasonable to expect that various amides formed from these fatty acids with amines (or amino alcohols or amino acids) would be biosynthesized and will play specific roles. Anandamide is one of the many possible amides. Esters can also be formed. 2-AG is one example. While anandamide and 2-AG have been investigated thoroughly, many of the other possible conjugates are still to be identified in the body and their roles have to be elucidated. Such compounds have been known for many years, but we may have seen just the tip of the iceberg of the existence and activities of such compounds. For instance, only recently palmitoyl ethanolamide was shown to be anti-inflammatory, oleoylamide is an endogenous sleep-inducing and possibly an anticonvulsant, arachidonoyl glycine lowers pain. Many other examples have been reported. It seems that the discovery of anandamide and 2-AG has opened a wide door towards a field of novel compounds, which may turn out to be of central importance in physiology.

The spectacular advances in the field of endocannabinoids promise to usher in an unprecedented era of research leading to wider understanding of biological systems and treating disease.

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