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The discovery of endogenous cannabinoids

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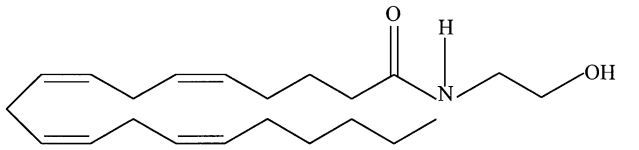
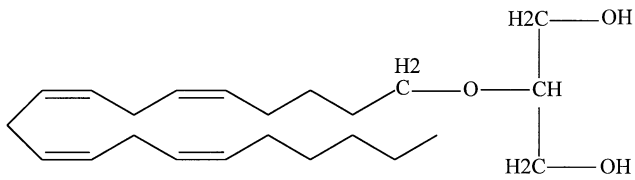
Throughout history, plant-derived substances have been used to induce healing, pleasurable feelings, or as poisons to kill or incapacitate. It was not until the second half of this century that the specificity of such effects has been attributed to the involvement of specific cellular receptors. In some cases, the targets turned out to be receptors for important signaling molecules, such as the nicotinic cholinergic receptor being the target for curare. The discovery of high affinity opiate receptors in the brain posed the dilemma of an age-old botanical impersonator (morphine) whose mammalian model has remained incognito until the discovery of endogenous opioid peptides, which represented the first example of a receptor serving as a tool in the discovery of its ligand.

Cannabis has been used since prehistoric times for its mood altering properties, but its main psychoactive ingredient, Δ^9-tetrahydrocannabinol (THC), was only identified in 1964 [4]. This was a critical advance, as the subsequent study of THC analogs revealed tight structure-activity relationships, an unmistakable sign of the involvement of specific receptors. Cannabinoid receptors were then identified by ligand binding and two receptors have been cloned. Thus, the stage was set for the key question: what is the physiological ligand of these receptors? Although the precedent of opioid peptides was alluring, the hydrophobic nature of plant-derived cannabinoids led Raphael Mechoulam to suspect that, in this case, the endogenous ligand may be a lipid. This was confirmed by the isolation from porcine brain of arachidonyl ethanolamide, named anandamide, which binds with high affinity to the brain (CB1) cannabinoid receptor and mimicks many of the neurobehavioral effects of THC [2].

Although only time will tell the true importance of this momentous discovery, the last few years have seen spectacular progress in our knowledge about endocannabinoids. In addition to anandamide and some related N-acyl-ethanolamides, 2-arachidonyl glyceride (2-AG) has also been identified as an endogenous ligand ([5,8; see Fig. 1). Both anandamide and 2-AG are present in brain as well as in some peripheral tissues, and evidence for their stimulation-induced release from neurons suggests a neurotransmitter/neuromodulator function [7]. A pathway has been identified for the biosynthesis of anandamide through the transacylation and phospholipase D-dependent cleavage of membrane phospholipid precursors [3]. Inactivation of anandamide by enzymatic degradation or by a specific cellular uptake mechanism has also been documented [3]. The introduction of a high affinity, selective CB1 receptor antagonist, SR141716A, has provided a tool for the identification of physiological processes modulated by endocannabinoids [6]. Surprisingly, there is little evidence to date for the tonic control of central neural functions by endocannabinoids. Although treatment with SR141716A alone has been reported to cause changes in certain neural functions opposite to those produced by cannabinoids, interpretation of such findings is complicated by the inverse agonist activity of SR141716A. Unexpectedly, endocannabinoids may have physiological functions outside the CNS, such as in pain initiation [1] or the local regulation of vascular tone [9]. Although endocannabinoids were discovered through their interaction with the CB1 receptor, there are indications of as-yet-unidentified endocannabinoid receptors [10] and there may be additional endogenous ligands. Thus, further secrets of this intriguing signaling system may unfold in the new millenium.



ANANDAMIDE



2-ARACHIDONYL GLYCERIDE

FIG. 1. The structure of the endocannabinoids anandamide and 2-arachidonyl glyceride.

REFERENCES

1. Calignano, A.; La Rana, G.; Giuffrida, A.; Piomelli, D. Control of pain initiation by endogenous cannabinoids. Nature 394:277–281; 1998.

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2. Devane, W. A.; Hanus, L.; Breuer, A.; Pertwee, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258:1946–1949; 1992.
3. Di Marzo, V.; Fontana, A.; Cadas, H.; Schinelli, S.; Cimino, G.; Schwartz, J.-C.; Piomelli, D. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature 372:686–691; 1994.
4. Gaoni, Y.; Mechoulam, R. Isolation, structure, and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. 86:1646–1647; 1964.
5. Mechoulam, R.; Ben-Shabat, S.; Hanus, L.; Ligumsky, L.; Kaminski, N. E.; Schatz, A. R.; Gopher, A.; Almog, S.; Martin, B. R.; Compton, D. R.; Pertwee, R. G.; Griffin, G.; Bayewitch, M.; Barg, J.; Vogel, Z. Identification of an endogenous 2-monglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem. Pharmacol. 50:83–90; 1995.
6. Rinaldi-Carmona, M.; Barth, F.; Heaulme, M.; Shire, D.; Callandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Meliat, J.; Caput, D. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett. 350:240–244; 1994.
7. Stella, N.; Schweitzer, P.; Piomelli, D. A second endogenous cannabinoid that modulates long-term potentiation. Nature 388:773–778; 1997.
8. Sugiura, T.; Kondo, S.; Sukagawa, A.; Nakane, S.; Shinoda, A.; Itoh, K.; Yamashita, A.; Waku, K. 2-Arachidonoylglycerol: A possible endogenous cannabinoid receptor ligand in brain. Biochem. Biophys. Res. Commun. 215:89–97; 1995.
9. Wagner, J. A.; Varga, K.; Ellis, E. F.; Rzigalinski, B. A.; Martin, B. R.; Kunos, G. Activation of peripheral CB1 cannabinoid receptors in haemorrhagic shock. Nature 390:518–521; 1997.
10. Wagner, J. A.; Varga, K.; Járai, Z.; Kunos, G. Mesenteric vasodilation mediated by endothelial anandamide-receptors. Hypertension 33[part II]:429–434; 1999.