Forum Minireview

New Perspectives in the Studies on Endocannabinoid and Cannabis: Preface

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Derivatives of *cannabis sativa*, such as marijuana and hashish, are the most widely consumed illicit drug in humans. Initial studies on cannabis have begun to clarify the mechanism of action of its psychoactive compounds such as Δ^9-tetrahydrocannabinol (Δ^9-THC), and investigations have mainly focused on the elucidation of the unique abnormal behavior. As recently as the early 1980s, behavioral effects were believed to be mediated by the ability of the drug to alter the fluidity and permeability of a cell's membrane through a nonspecific mechanism, based on its very high lipophilicity. In 1988, it was found that cannabinoid compounds induce their pharmacologoical effects by activating two different receptors that have been identified and cloned: the cannabinoid CB_1 receptor (cloned in 1990), which is highly expressed in the CNS, and the cannnabinoid CB_2 receptor (cloned in 1993), which is located in the peripheral tissues, mainly at the level of the immune system. Moreover, potential endocannabinoids such as anandamide and 2-arachidonoylglycerol (2-AG) and the pathway for their biosynthesis have been identified. By these discoveries, cannabinoid research has changed direction to the elucidation of the functional role of cannabinoid receptor/endocannabinoid in the organism.

In 2004, "New Perspectives in the Studies on Endocannabinoid and Cannabis" was adopted as a symposium topic for the first time in The Japanese Pharmacological Society's 77th Annual Meeting (Osaka, March 9, 2004), and the significant advances within each field were discussed. This forum minireview is based on papers presented in this symposium.

By in vitro experiments, Fujiwara et al., who co-chaired the symposium with myself, revealed that the behavioral effect of Δ^9-THC, using an animal model of multiple sclerosis and spatial-memory task, is mediated by the inhibition of glutamate release. They mentioned that a Δ^9-THC analog might provide an effective treatment for psychosis and neurodegenerative diseases.

Sugiura, focusing on physiological roles of endogenous cannabinoid receptor ligands, strongly suggested that 2-AG plays an essential role in the stimulation of various inflammatory reactions in vivo.

The standpoint of the cannabinoid hypothesis for pathogenesis of schizophrenia introduced by Ujike is unique: he demonstrated that the 9-repeat allele of the AAT repeat polymorphism of the CNR1 gene may be the risk factor for the susceptibility to hebephrenic schizophrenia.

From the view point of the involvement of the cannabinoid system in mediating drug reward and relapse to drug taking, Yamamoto et al. indicated that the endocannabinoid-arachidonic acid pathway may be an important part of the neural machinery underlying drug addiction.

Finally, I would be happy if these reviews could help to promote studies of cannabinoid/cannabinoid CB receptors and lead to clinical use of cannabinoid-related compounds.

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