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Allergic Contact Dermatitis and the Endocannabinoid System: From Mechanisms to Skin Care

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The cloning of the first cannabinoid receptor followed by the discovery of one of the major endocannabinoids, anandamide, at the beginning of the nineties, are two important milestones of the cannabinoid research. Since that, in a quite short period of time, the knowledge of the endocannabinoid system has massively increased[1] and its implications in health and disease have been widely explored.[2,3] The set of biosynthetic enzymes, of endocannabinoids themselves, of molecular targets (at the membrane and in the nucleus), and of endocannabinoid hydrolyzing enzymes nowadays considered part of the endocannabinoid system is continually expanding. Regarding the molecular targets, at the membrane level, two G protein-coupled receptors, that is, the CB_1 cannabinoid receptor and the CB_2 cannabinoid receptor, seem to mediate most of the effects of endocannabinoids and exogenous cannabinoids. A nonselective cation channel, the transient receptor potential vanilloid type 1 ($TRPV_1$) has been proposed to mediate some of the effects of anandamide and of some *N*-acylethanolamines.[4] In the nucleus, cannabinoids may interact to some extent with two peroxisome proliferator-activated receptors—PPAR-α and PPAR-γ—and regulate fatty acid metabolism and inflammation.[5] Several enzymes participate in the termination of endocannabinoid signaling. Four hydrolases have been cloned, namely and in chronological order of their cloning, fatty acid amide hydrolase (nowadays termed FAAH-1),[6] monoacylglycerol lipase (MAGL),[7,8] *N*-acylethanolamine acid amidase (NAAA),[9] and a fatty acid amide hydrolase-2 (FAAH-2).[10] Based on the the diverse components of the endocannabinoid system and taking into account the wide distribution of the molecular targets, a therapeutic endocannabinoid-based strategy could be useful in numerous and diverse pathological conditions: mood and anxiety disorders, movement disorders such as Parkinson's and Huntington's diseases, inflammatory and neuropathic pains, multiple sclerosis and spinal cord injury, cancer, atherosclerosis and cardiovascular diseases, stroke, glaucoma, obesity and metabolic syndrome, addictions (tobacco, alcohol, drug of abuse), and osteoporosis are among the most cited in the literature.[2,3] Blocking the CB_1 cannabinoid receptor presents several therapeutic outcomes. Rimonabant from Sanofi-Aventis was the first CB_1 receptor antagonist to enter clinical trials. It has been now approved in 42 countries and marketed in 20 to treat obesity and overweight patients with associated cardiovascular risk factors.[11,12] Other indications have been identified for this class of compounds such as treatment of addiction (smoking, alcohol, and drug addictions),[13] hepatic diseases such as liver fibrosis,[14] chronic bronchitis and chronic obstructive bronchopneumopathy,[15] inflammation, and arthritis.[16] Considerable medicinal chemistry endeavors have been pursued in the last ten years, mainly seeking CB_1 cannabinoid receptor antagonists, selective CB_2 cannabinoid receptor agonists, and inhibitors of endocannabinoid hydrolysis. Despite the fact that some cannabinoid drugs are marketed, psychoactive effects mediated by CB_1 receptors hamper a wide use of CB_1 agonists as pain killers, and restrict them to treating nausea and vomiting associated with cancer chemotherapy or to promote appetite in acquired immunodeficiency syndrome patients. In the June eighth issue of Science, Karsak et al.[17] have explored a poorly investigated area: the endocannabinoid system appears to elicit a protective role in allergic contact dermatitis. In industrialized countries, contact allergy affects nearly 10–15% of population, women seem to be more sensitive than men. Sensitization is caused by skin contact with low molecular-weight haptens, which after repeated allergen contacts induce recruitment of T cells, leading to the production of inflammatory cytokines and chemokines. Risk factors include the sensitizing potential of an allergen, elevated allergen concentration, high frequency of and duration exposure, occlusion, the presence of penetration-enhancing factors, and an altered skin barrier function. Before this study, little was known about the role of cannabinoid receptors in skin, even though both CB_1 and CB_2 have been described on keratinocytes.[18,19] Dvorak et al. noticed in humans that peripheral administration of a nonselective CB_1-CB_2 agonist by skin patch or dermal microdialysis attenuated histamine-induced itch.[20] Blázquez et al.[21] recently evidenced that activation of the CB_1 and CB_2 cannabinoid receptors present in human melanomas and melanoma cell lines decreased growth, proliferation, angigogenesism, and metastasis, and increased apoptosis of melanomas in mice, suggesting a potential cannabinoid therapy for this type of cancer. The working hypothesis of Karsak and colleagues

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raised from an intriguing observation in mice lacking both CB_1 and CB_2 cannabinoid receptors (here termed double-knockout mice). The double-knockout colony—in contrast to single CB_1 deficient mice or to single CB_2 deficient mice—presented skin ulcerations and scratching behaviour when bearing nickel-containing ear tags. In mice exhibiting ulcerations, histopathological analyses suggested an allergic reaction with intense mast cells infiltration. To confirm this observation, a contact allergen challenge using 2,4-dinitrofluorobenzene was conducted in the three mice populations. Contact allergy was observed in both single knock-out and double knock-out mice. Administration of cannabinoid antagonists on wild-type mice gave similar results and in contrast, treatment with Δ^9-tetrahydrocannabinol attenuated the dermatitis. During the experimental allergy contact dermatitis, levels of endocannabinoids were increased, and a downregulation of CB_1 cannabinoid receptors was observed whereas CB_2 cannabinoid receptors were upregulated. The involvement of the cannabinoid CB_2 receptor has been previously suggested by Oka et al.[22] in another model of contact dermatitis in mice induced by topical administration of oxazolone on the ear five days after first sensitization. The levels of 2-arachidonoylglycerol were increased in mouse ear with oxazolone-induced contact dermatitis in contrast to those of *N*-acylethanolamines, including anandamide, which remain unaffected. The administration of a cannabinoid CB_2 receptor inverse agonist, SR144528, reduced the ear swelling and the production of different proinflammatory cytokines. Similarly, Maekawa et al. reported the antipruritic activity of JTE-907, a cannabinoid CB_2 receptor inverse agonist, in atopic dermatitis.[23] The fact that Karsak et. al[17] observed that cannabinoid CB_2 receptor knock-out mice or a cannabinoid CB_2 receptor antagonist administration can worsen the 2,4-dinitrofluorobenzene-induced dermatitis gives a puzzling picture, where both cannabinoid CB_2 receptor antagonists and cannabinoid CB_2 receptor agonists seem to be active against active contact dermatitis. A possible explanation might originate from the fact that activation of the cannabinoid CB_2 receptor can produce chemotaxis and attract or remove inflammatory cells from a site, depending on where in the body CB_2 cannabinoid receptor are being activated. However this seducing hypothesis remains to be investigated. As the levels of endocannabinoids were increased, the authors investigated the development of experimental allergy contact dermatitis in mice lacking FAAH-1 which exhibit elevated levels of anandamide. A significant decrease of the allergy was observed suggesting the potential of fatty acid amide hydrolase inhibitors in skin inflammation. Finally, a microarray analysis indicated that immune-related genes are modified. Among them, the monocyte chemotactic protein 2/chemokine (C-C motif ligand 8) appears to play a key role in the endocannabinoid mediated skin responses.

In conclusion, substantial evidence has been accumulated in this study indicating the role of the endocannabinoid system in the attenuation of the experimental allergy contact dermatitis. It opens the way for further pharmacological treatments with cannabinoid agonists or inhibitors of endocannabinoids hydrolysing enzymes. Regarding the general lipophilicity of such agents, topical application including transdermal delivery[24] could be readily achieved.

Keywords: allergy · CB_1 cannabinoid receptor · CB_2 cannabinoid receptor · fatty acid amide hydrolase · keratinocytes

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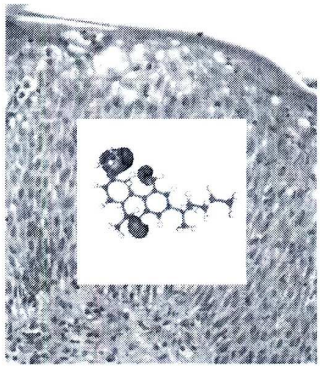

A therapeutic endocannabinoid-based strategy could be useful in numerous and diverse pathological conditions, including CNS disorders, cancer, and cardiovascular diseases. However, Karsak et al. have explored a poorly investigated area: the endocannabinoid system and its abilitly to elicit a protective role in allergic contact dermatitis. Herein, the significance of this work is discussed.

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