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Anti-inflammatory And Anti-pruritic Effects Of WO20100083-440, A Novel, Potent Inhibitor Of FAAH In A Murine Model Of Atopic Dermatitis

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A functional endocannabinoid system (ECS) has been described in skin. By increasing the endocannabinoid tone in skin and thereby suppressing immune or inflammatory responses it might be possible to treat inflammatory diseases like atopic dermatitis (AD), for which an unmet medical need exists. The mainstay therapies topical corticosteroids and calcineurin inhibitors are effective. However, their use, especially for chronic treatment, is limited by side effects or due to a black box warning. Thus, a topical treatment with similar efficacy and a superior safety profile has a high potential to become the treatment of choice of AD and other inflammatory and pruritic skin diseases, especially for children. The aim of this study was to test the potential therapeutic properties of a topical FAAH inhibitor in a mouse model of AD.

Methods: The novel, potent FAAH inhibitor WO20100083-440 was tested in NC/Nga mice, an inbred mouse strain that develops a spontaneous AD-like pathology in non-sterile housing conditions (Matsuda H et al, Int Immunol 9:461, 1997). Male mice (n=8-9) were exposed to dust mite antigen and randomized prior to the start of the study on the basis of the average total clinical disease score (approximately 1) consisting of erythema (0–3), edema or papulations (0–3) and oozing, crusts or hemorrhages (0–3). Mice received a single daily topical dose of vehicle (20 µL, acetone/olive oil (4:1)) or WO20100083-440 (20 µL, 1% (w/v) in acetone/olive oil (4:1)) that was applied to the back area for 30 days. Hydrocortisone butyrate (20 µL, 0.1% (w/v) in acetone/ olive oil (4:1)) and 0.1% Protopic® (10 mg/cm^2) were used as positive controls. Clinical score and ear thickness were assessed twice weekly. Scratching was measured at day 0 (baseline) and day 30.

Results: In non-treated mice an increase of the total clinical score of 1.9 was observed from day 1 to day 30. Treatment with WO20100083-440 resulted in a moderate but significant ($p<0.01$, two-way repeated measure ANOVA followed by Bonferroni posttest) decrease of 0.55 of the total clinical score. The effect was comparable to the one obtained for hydrocortisone butyrate and Protopic®. Treatment with WO20100083-440 significantly ($p<0.05$) inhibited ear swelling from day 11 onwards. Moreover, a significantly ($p<0.05$, two-tailed T-test) decreased scratch number was observed for treated mice on day 30 vs. baseline, whereas in the vehicle control a trend ($p=0.056$) towards higher scratch numbers was seen.

Conclusions: These results support the idea that the ECS is significantly involved in inflammatory response in skin. Modulation of the ECS by a FAAH inhibitor resulted in anti-inflammatory and anti-pruritic effects in NC/Nga mice. Thus, FAAH inhibitors should be explored in detail as potential drugs for the treatment of cutaneous inflammatory diseases like atopic dermatitis.

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