

POSTER PRESENTATIONS

THERAPEUTIC TARGETING OF TRPV3 CHANNEL WITH PLANT DITERPENOID 14-DEOXY-11,12-DIDEHYDROANDROGRAPHOLIDE

A.P. Kalinovskii, Y.A. Andreev

*Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of
Sciences, 117997, Ul. Miklukho-Maklaya, 16/10, Moscow, Russia*

TRPV3 is a calcium-permeable heat- and ligand-activated channel that acts as a molecular integrator of cell function in epidermal keratinocytes. TRPV3 is robustly implicated in skin physiology, e.g., skin and hair renewal, and pathology, e.g., atopic dermatitis, pruritus, alopecia, cutaneous lupus erythematosus, and genetic keratoderma (Olmsted syndrome). Moderate activation of TRPV3, e.g. with essential oils, can be beneficial for keratinocyte and hair follicle homeostasis. However, intervention with selective TRPV3 inhibitors can present an effective means of the skin inflammation management where TRPV3 function is excessively upregulated. Plants serve as a rich source of TRPV3 activators and inhibitors with diverse chemotypes, therefore, we focused on the testing of the plant extracts.

We investigated a labdane-type diterpenoid 14-deoxy-11,12-didehydroandrographolide (DDA), which we isolated from the *Andrographis paniculata* extract using TRPV3-targeted bioassays. DDA inhibited human TRPV3 expressed in CHO and keratinocytes HaCaT, and acted selectively in comparison to TRPV1, TRPV4, and TRPA1. We discovered a modality-selective action of DDA that acts as a competitive antagonist to cannabidiol-evoked activation of the channel (IC₅₀ 7 nM), negative allosteric modulator to 2-APB-evoked activation (IC₅₀ 0.87 μM), and does not affect the activation evoked by innocuous heat (25–43 °C). Mechanistically, as we show with molecular docking and site-directed mutagenesis, DDA binds within the vanilloid pocket in the transmembrane region of TRPV3 and shares its site with cannabidiol. DDA principally interacts with L557 and L664 via hydrophobic interactions while cannabidiol interacts with A560 and L664.

Next, we tested DDA against skin pruritus in mice. DDA suppressed the number of scratching bouts induced by the TRPV3 activator carvacrol. Notably, it was also highly effective against the histamine-induced pruritus acting on the same level as the clinical antihistamine drug loratadine. In sum, our data support the high potential of DDA as a TRPV3-targeting experimental therapeutic.

This study was funded by Russian Science Foundation, project # 26-15-00046.