Activation of retinoic acid-related orphan receptor γ(t) by parabens and benzophenone UV-filters.

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Retinoic acid-related orphan receptor γt (RORγt) regulates immune responses and its impaired function contributes to inflammatory and autoimmune diseases and may promote skin cancer. Synthetic inverse RORγt agonists block the production of Th17-associated cytokines including interleukin (IL)-17A and IL-22 and are under investigation for treatment of such pathologies. Unintentional RORγt activation in skin, following exposure to environmental chemicals, may promote inflammatory skin disease. Parabens and UV-filters, frequently used as additives in cosmetics and body care products, are intensively inspected for endocrine disrupting properties. This study assessed whether such compounds can interfere with RORγ activity using a previously established tetracycline-inducible reporter gene assay in CHO cells. These transactivation experiments revealed hexylparaben, benzylparaben and benzophenone-10 as RORγ agonists (EC; 50; values: 144ăśă97ănM, 3.39ăśă1.74ăţM and 1.67ăśă1.04ăţM, respectively), and they could restore RORγ activity after suppression by an inverse agonist. Furthermore, they enhanced RORγt-dependent transcription of the pro-inflammatory IL-17A and/or IL-22 genes in the murine T-cell model EL4. Virtual screening of a cosmetics database for structurally similar chemicals and in vitro testing of the most promising hits revealed benzylbenzoate, benzylsalicylate and 4-methylphenylbenzoate as RORγ agonists (low micromolar EC; 50; values). Moreover, an analysis of mixtures of the newly identified RORγ agonists suggested additive effects. This study presents novel RORγ(t) agonistic structural scaffolds. By activating RORγ(t) the identified parabens and UV-filters may potentially aggravate pathophysiological conditions, especially skin diseases where highest exposure of such chemicals can be expected. Follow-up studies should assess whether such compounds, either alone or as mixtures, can reach relevant concentrations in tissues and target cells to activate RORγ(t) in vivo.

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