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Design of a Cooling TRPM8 agonist to treat ocular discomfort

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Ocular discomfort is common because the eye surface has a high density of sensory nerve endings. Current methods for rapid (<5 min) and prolonged (>2 hr) relief of symptoms such as irritation, dryness, asthenopia, pruritus, and pain are limited. Physical cooling of the eye surface relieves ocular discomfort, but translating this event to drug treatment has not been much studied. TRPM8, an ion channel target on nerve endings, is associated with sensations of cooling and cold and was chosen here as drug target for screening lead candidates. The agonists called 1-dialkylphosphorylalkanes (Dapa) were chosen as the best source of prototypes by contrast to e.g. icilin, p-menthane carboxamides, p-menthane esters. In the design of an ideal agent, the goals are to select the correct target, and to deliver the right molecule to the right place at the right time. Dense TRPM8 innervation was found on the mouse eyelid and cornea, but not on the conjunctiva. The eyelid receptors were selected as drug targets. Lead candidates potently and selectively activate TRPM8 (linked to cooling) but not TRPV1 or TRPA1 (linked to nociception). A prototype Dapa called cryosim-3 (C3) was tested in subjects with mild forms of dry eye disease (BMC Ophthalmology 2107). C3 applied to upper eyelids (n=30) elicited cooling sensations, lasting 46 min and increased tear secretion. C3, 2 mg/mL in water, or water in a single-unit dispenser was applied 4x times daily for 2 weeks (n=20 per group) and data analyzed before and at 1 and 2 weeks thereafter. In questionnaire surveys of ocular discomfort indices (VAS scale, OSDI, and CVS symptoms), the C3 treatment group clearly showed improvement of symptoms at one and two weeks and an increase of basal tear secretion. No signs of irritation or pain were reported. C3 is a promising candidate for relief of ocular discomfort.

Biography

Edward T Wei received his PhD in Pharmacology at the University of California San Francisco Med Center in 1969. He pursued Post-doc at Stanford University in 69-70, then joined the Faculty at University of California at Berkeley, and retired from active teaching in 2010. He discovered the cooling properties of icilin and gave this molecule its name. He uses the intellectual property medium to express creativity. He is active in drug discovery and development.

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