Sensory/Cooling Agents for Skin Discomfort

Edward T. Wei

University of California, Berkeley, CA 94720, USA

Heat abstraction from the body’s surfaces can refresh the senses, relieve discomfort, attenuate pain, and suppress inflammation. Sensory/cooling agents are molecules that can mimic these effects without a change in tissue temperatures. Menthol is a familiar sensory agent used on the aerodigestive tract and on the skin, but its limited duration of action and side-effects are well known. Icilin is an excellent cooling agent for the mucous membranes but difficult to formulate for delivery to the skin. A number of p-menthane carboxamides have been created and show promise as novel anti-pruritic drugs. Molecules that simulate the effects of heat abstraction are termed “cryosims” to help distinguish them from menthol.

Key Words: Cooling, Cold, Menthol, Icilin, Skin, Cryosim

Introduction

Abstraction of heat from body surfaces evokes sensations that are termed cool, refreshing cool, chilly, cold, icy cold and painful cold. Chemical sensory/cooling agents are molecules that can mimic these sensations without a change in tissue temperatures. The exact sensations produced by chemicals depend on the selection of the active ingredient and the site and method of delivery. In response to chemicals, the mucosa of the ocular, oral cavity, pharyngeal and anogenital surfaces are able to discriminate between subtleties in sensations, but the tongue and skin give more ambiguous descriptors of the perceived effect. Chemical cooling on the scalp and skin of the face, nostrils, philtrum, neck, shoulder blades, and ankles can be elicited, but the effects do not last long. For the skin of the torso and limbs overt, localized, and sustained sensations of coolness and cold are difficult to evoke.

In spite of the difficulty of getting prolonged cooling on skin with chemical agents, there is nevertheless the attractive prospect that discomfort from irritated and inflamed skin that occurs, for example, from eczema, psoriasis, or xerosis, can be relieved and managed with a sensory/cooling agent. One major question is how to create and to assay chemicals that might have utility in therapy.

Active Ingredients: Menthol, Icilin

Menthol is a familiar agent of human experience. It is a molecule with multi-faceted pharmacological actions. Examination of menthol’s effects gives insight into the design of new active ingredients.

Menthol has been called “promiscuous” because its molecular targets include agonist actions at Trp-M8 and Trp-V3 and antagonist action at Trp-A1. On the face, and in the aerodigestive tract, the receptive fields for menthol are located on afferents of the olfactory (1st), trigeminal (5th), facial (7th), glossopharyngeal (9th) and vagus (10th) cranial nerves. Sensations can be “confusing” when a chemical has multimodal action on sensory processes and the receptive fields are widely distributed. This is especially true for menthol which is a strong irritant on the ocular surface, has a minty odor in the nose, a harsh and bitter taste on the tongue, and a cooling sensation as a vapor in the nasopharynx and
upper airways. When used in strong mints, mouth washes, or toothpaste, menthol acts on the tongue and buccal mucosa to elicit somatosensation (numbness, cooling, irritation, tingling) and gustation (bitter). In the nose and oral cavity, the predominant mode of detecting menthol is olfactory. The cooling sensations of mint candies such as Mentos in the nasal cavity also come from retronasal delivery of volatilized menthol in the breath onto membranes of the nose and nasopharynx. Individuals who have smoked Salem or Kool cigarettes know that the smoke produces strong sensations in the back of the mouth and on the pharynx. Here the dose of menthol delivered is ~62 μg/puff and the average 10 puffs/cigarette yields a fresh sensation in the upper airways.

On the skin, menthol has local anesthetic actions and can also be used as a counter-irritant. For example, 5 to 10% menthol can be applied to skin as an ointment or a patch to counteract muscle pains. The absorbed menthol can be felt in the ureter when the menthol is excreted in the urine. The anti-pruritic effects of menthol solutions have not been documented in placebo-controlled studies. In a rare well-designed study, Yosipovitch et al. applied 100 mg of menthol (in a 1 ml volume) onto the flexor surface of the forearms of 18 volunteers. Menthol was dissolved in 80% ethanol-10% deionized water. 12/18 subjects reported cooling sensations lasting on average 32 min, vs 4/18 for vehicle alone, but 8/18 subjects also complained of burning sensations lasting up to 40 min! In this study, histamine-induced itch and pain were not attenuated by menthol. Similar results were found by Hatem et al. who noted the possible confounding effects of using ethanol as the solvent of menthol. Clearly, menthol has a complex spectrum of sensory effects on the skin.

Menthol has a molecular weight of 156 Daltons, a melting point of ~42ºC, and a log Kow of 3.4. These properties facilitate rapid distribution of menthol away from the site of application.

Fig. 1. Chemical structures of sensory/cooling agents. A. icilin, B. to G. p-menthane carboxamides and H. (R)-1,2-propanediol.