The Odorant (R)-Citronellal Attenuates Caffeine Bitterness by Inhibiting the Bitter Receptors TAS2R43 and TAS2R46

Abstract:
Sensory studies showed the volatile fraction of lemon grass and its main constituent, the odor-active citronellal, to significantly decrease the perceived bitterness of a black tea infusion as well as caffeine solutions. Seven citronellal-related derivatives were synthesized and shown to inhibit the perceived bitterness of caffeine in a structure-dependent manner. The aldehyde function at carbon 1, the (R)-configuration of the methyl-branched carbon 3, and a hydrophobic carbon chain were found to favor the bitter inhibitory activity of citronellal; for example, even low concentrations of 25 ppm were observed to reduce bitterness perception of caffeine solution (6 mmol/L) by 32\%, whereas (R)-citronellic acid (100 pm) showed a reduction of only 21\% and (R)-citronellol (100 pm) was completely inactive. Cell-based functional experiments, conducted with the human bitter taste receptors TAS2R7, TAS2R10, TAS2R14, TAS2R43, and TAS2R46 reported to be sensitive to caffeine, revealed (R)-citronellal to completely block caffeine-induced calcium signals in TAS2R43-expressing cells, and, to a lesser extent, in TAS2R46-expressing cells. Stimulation of TAS2R43-expressing cells with structurally different bitter agonists identified (R)-citronellal as a general allosteric inhibitor of TAS2R43. Further structure/activity studies
indicated 3-methyl-branched aliphatic aldehydes with a carbon chain of $\geq 4$ C atoms as best TAS2R43 antagonists. Whereas odor-taste interactions have been mainly interpreted in the literature to be caused by a central neuronal integration of odors and tastes, rather than by peripheral events at the level of reception, the findings of this study open up a new dimension regarding the interaction of the two chemical senses.