Ginger and its pungent constituents non-competitively inhibit activation of human recombinant and native 5-HT3 receptors of enteric neurons.

Abstract:
Beneficial effects of ginger in the treatment of gastrointestinal (GI) problems and chemotherapy-induced nausea and vomiting are well accepted. In rodents, the action of ginger seems to be mediated by the inhibition of 5-HT3 receptors, which are established targets to combat emesis and irritable bowel syndrome. Heterologously expressed human 5-HT3 A or 5-HT3 AB receptors were characterized by means of Ca(2+) influx studies using HEK293 cells. Complementing Ca(2+) measurements in Fluo-4-AM-stained whole-mount preparations of the human submucous plexus were carried out. Furthermore, [3H]GR65630 binding assays were performed to reveal the mode of action of ginger and its pungent compounds. We show for the first time that ginger extracts and its pungent arylalkane constituents concentration-dependently inhibit activation of human 5-HT3 receptors. Ginger extracts inhibited both receptors with increasing content of pungent compounds, confirming that these are part of ginger's active principle. Inhibition potencies of the arylalkanes 6-gingerol and 6-shogaol on both receptors were in the low micromolar range. A lipophilic ginger extract and 6-gingerol had no influence on 5-HT potency, but reduced the 5-HT maximum effect, indicating non-competitive inhibition. The non-competitive action was
confirmed by [(3) H]GR65630 binding, showing that the ginger extract did not displace the radioligand from 5-HT3 A and 5-HT3 AB receptors. The potential relevance of the inhibitory action of ginger on native 5-HT3 receptors in the gut was confirmed in whole-mount preparations of the human submucous plexus. While a general neurotoxic effect of 6-gingerol was ruled out, it inhibited the 2-methyl-5-HT-mediated activation of 5-HT3 receptors residing on enteric neurons. Our findings may encourage the use of ginger extracts to alleviate nausea in cancer patients receiving chemotherapy and to treat functional GI disorders.