

Mini Review





# Taste receptors type 2 would not mediate bitter tastant-induced relaxation of airway smooth muscle

#### **Abstract**

Recently, it has been found that taste receptors type 2 (TAS2R) are expressed in airway smooth muscle (ASM) cells and their activators bitter tastants inhibit ASM contraction induced by agonists. In this mini review, we summarized the progress in understanding of bitter Tastant-induced ASM relaxation. We also mentioned the inhibitory action and the underlying mechanism of bitter tastants extracted from bitter herbs. These recent findings indicate that bitter tastants would be a novel class of bronchodilators for the treatment of obstructive lung diseases such as asthma and chronic obstructive pulmonary disease (COPD)

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# Mechanism of bitter tastant-induced relaxation

Taste receptors type 2 (TAS2R) are responsible for detecting bitter sensation,1 which have recently been found to be expressed in ASM cells and which mediate inhibition on the pre contraction through large-conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channels (BKs).<sup>2,3</sup> However, our and others' results indicate that the relaxation would not be mediated by BKs, which will result from the inhibition of L-type voltage-dependent Ca2+ channels (LVDCCs) and non-selective cat ion channels (NSCCs).4-7 These studies clarified the paradox about the mechanism of bitter Tastant-induced relaxation. Bitter tastants induce Ca2+ store release leading to cytosolic Ca2+ increases through the TAS2R- $G_{\beta\gamma}$  protein-PLC $\beta$ -IP $_3$ -IP $_3$ R pathway, however, the increased Ca2+ does not cause a contraction.5,8 This would be because that the increase of Ca2+ did not reach the threshold level of triggering a contraction, which might be due to that bitter tastants inhibited Ca<sup>2+</sup> release channels such as ryanodine receptors (RyRs) and IP3 receptors (IP3Rs), since that bitter tastants blocked caffeine (an activator of RyRs)-induced cytosolic Ca2+ increases7 and ACHinduced Ca2+ oscillations mediated by IP,R-induced Ca2+ release.9,10 Thereby, bitter Tastant-induced Ca2+ release would be inhibited, leading to that the cytosolic Ca2+ cannot increase to the level for evoking a contraction.

However, the agonist ACH-induced the Ca<sup>2+</sup> release from the intracellular store mediated by IP<sub>3</sub>Rs will not be inhibited, thereby, which leads to a depletion of the store to activate SOC (store-operated channels) such as the NSCCs.<sup>6</sup> In addition, ACH (or methacholine) also activates LVDCCs.<sup>5,6</sup> This Ca<sup>2+</sup> per meant ion channels will then mediate Ca<sup>2+</sup> influx, resulting in a sustained contraction. If these channels were blocked by bitter tastants, the pre contraction will then be inhibited.<sup>5,6</sup>

Overall, bitter tastants induce Ca<sup>2+</sup> increases through activating intracellular ion channels by the TAS2R-mediated signal pathway, however, the channels are then directly inhibited by bitter tastants, thereby, the Ca<sup>2+</sup> elevations are observed and the resultant contraction is not noted. Except for inhibiting these intracellular ion channels, bitter tastants can also inhibit the plasma ion channels activated by the Ca<sup>2+</sup> store depletion, which then leads to a reduction of intracellular Ca<sup>2+</sup> and eventually induces a relaxation. Thus, this relaxation induced by bitter tastants would not be mediated by the TAS2Rs.

# Bitter tastants as new bronchodilators

Above results indicate that bitter tastants would be potent bronchodilators, which can be used to treat obstructive lung diseases such as asthma and COPD, <sup>11–16</sup> particularly based on that bitter tastants inhibit the pre contraction of human ASM. <sup>14,15</sup> However, the inhibitory action of bitter tastants to ASM contraction might not be through the TAS2Rs on the basis of the above descriptions.

#### Relaxant action of herbal bitter tastants

We recently further extracted compounds from bitter herbs Plumula Nelumbinis<sup>17</sup> and Cortex phellodendri<sup>18</sup> and investigated their effects on ASM contraction. The extracts, which tasted bitter, inhibited ACH-induced pre contraction of mouse ASM by inhibiting LVDCCs and NSCCs, similar to that of the known bitter tastants used in the studies described above. Moreover, such relaxation was observed in tracheal and bronchial ASM from controls and mouse models of asthma, suggesting this bitter tastants-induced relaxation will be regardless of ASM locations and diseased ASM. Our results also indicate that, except for these two types of channels, there will be another pathway that mediates these extracted bitter tastants-induced relaxations. Since that following blockade of these channels, the remaining pre contraction was observed and then completely blocked by the extracts. The unknown pathway remains to be further defined. These findings suggest that bitter tastants from bitter herbs could also be used to develop new bronchodilators.

#### **Conclusion**

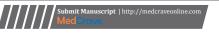
Bitter tastants induce intracellular  $Ca^{2+}$  increases through the TAS2R- $G_{\beta\gamma}$  protein-PLC $\beta$ -IP $_3$ -IP $_3$ R pathway, however, which also inhibit IP $_3$ R. Thereby, the  $Ca^{2+}$  increase would not be large enough to trigger a contraction. In addition, bitter tastants can inhibit plasma  $Ca^{2+}$  per meant ion channels activated by agonists, leading to the contraction to be inhibited, in which the TAS2Rs are not involved.

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# **Conflicts of interest**

Author declares there are no conflicts of interest.





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