Role of TRP Channels in CCK-Induced Activation of Cultured Vagal Afferent Neurons from Rat.

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The entry of fat and protein into the duodenum causes the release of cholecystokinin (CCK) from I-cells in the mucosal epithelium. CCK in turn acts to end further consumption of food via an effect that requires an intact vagus nerve. In prior studies we demonstrated that CCK can directly depolarize isolate vagal afferent neurons, but the identity of underlying conductances is unknown. In the present study, we postulate that one or more members from the transient receptor potential (TRP) ion channel family are involved in this CCK-induced activation. We employed patch-clamp electrophysiological recordings as well as intracellular calcium measurements to investigate the effects of agents that alter the behavior of TRP channels on CCK-induced responses on neurons isolated from rat nodose ganglia. We first tested a broad-spectrum TRP modulator lanthanum (La^{3+}), and observed mixed responses. In half the cells tested, 100 μM La^{3+} completely abolished or significantly attenuated the responses to CCK (20 nM), whereas in the other half, responses to CCK were either unaltered, or even potentiated. We then examined a relatively more selective TRP blocker ruthenium red (RuR; blocks TRPV1-4 and TRPA1) at both concentrations of 1 μM and 10 μM. We found that at the lower concentration, RuR abolished CCK-induced activation in nearly half the cells, but the block was incomplete in others. However, at the higher concentration, RuR specifically and consistently blocked responses to CCK. We further studied several specific TRP blockers including SKF96365 (TRPC blocker), SB366791 (TRV1 blocker), and HC030031 (TRPA1 blocker). They were either without effect or had only minor effect on CCK-induced responses, suggesting that TRPCs, TRPV1, and TRPA1 are unlikely to be the prime candidates for mediating CCK signaling in the nodose. Collectively, our findings strongly implicate that several TRP channels, specifically, TRPV2, TRPV3, and TRPV4, are important in CCK-induced activation of vagal afferents. Whether a particular subtype contributes more or all three subtypes are evenly involved requires future investigations.