The polyphenol ellagic acid exerts anti-inflammatory actions via disruption of store-operated calcium entry (SOCE) pathway activators and couplin g mediators

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Abstract

Ellagic acid, a naturally occurring phenol found in a variety of fruits and nuts has been shown to possess antiinflammatory properties. However, the mechanism of action behind its anti-inflammatory action is unclear. Using human Jurkat T cells, our study examined the effects of ellagic acid (EA) on Ca2+ handling, in particular, store-operated Ca2+ entry (SOCE), a process critical to proper T cell function. We observed that the acute addition of EA-induced Ca2+ release with an EC50 of 63 mu M. The Ca2+ release was significantly attenuated by Xestospongin C, a known inhibitor of the Inositol 1,4,5-trisphosphate receptor (IP3R) channel and was unaffected by the phospholipase C (PLC) inhibitor, U73122. Furthermore, chronic incubation of Jurkat T cells with EA not only decreased the ATP-induced Ca2+ release but also diminished the SOCE-mediated Ca2+ influx in a dose-dependent manner. This inhibition was confirmed by reduced Mn2+ entry rates in the EA-treated cells. The ATP-induced Ca2+ entry was also attenuated in EA-treated HEK293 cells transiently transfected with SOCE channel Orai1-myc and ER-sensor stromal interaction molecule (STIM1) (HEKSTIM/Orai). Moreover, EA treatment interfered with the Orai1 and STIM1 coupling by disrupting STIM1 puncta formation in the HEKSTIM/Orai rar cells. We observed that EA treatment reduced cytokine secretion and nuclear factor of activated T-cell transcriptional activity in stimulated T cells. Hence, by inhibiting SOCE mediated Ca2+ influx, EA decreased downstream activation of pro-inflammatory mediators. These results suggest a novel target for EA-mediated effects and provide insight into the mechanisms underlying EA-mediated anti-inflammatory effects.

Palabras clave

Palabras clave de autor: Ellagic acid; Store-operated calcium entry (SOCE); Stromal interaction molecule (STIM); Orai; Anti-inflammatory

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