Dehydrohispanolone derivative is a potent inhibitor of NLRP3 inflammasome activation.

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Abstract

The NLRP3 inflammasome is a multi-protein complex that plays a crucial role in the pathogenesis of several inflammatory diseases. It mediates caspase-1 activation leading to the maturation and secretion of pro-inflammatory cytokines IL-1β and IL-18 from cells of the innate immune system. Besides, caspase-1 activation also induces a type of cell death called pyroptosis. Despite being a potential target for the treatment of inflammatory diseases, there are no specific NLRP3 inhibitors available clinically to date. Among natural products, the bioactive diterpene hispanolone and its derivatives have shown anti-inflammatory effects. In the present study, we have evaluated the effects of a dehydrohispanolone derivative (N8) as NLRP3 inflammasome inhibitor and the molecular targets underlying its mechanism of action. The results revealed that N8 specifically blocked NLRP3 activation in J774A.1 macrophages. N8 significantly reduced IL-1β release and caspase-1 activity after activation by diverse stimuli (LPS + Nigericin, ATP or MSU), with an IC50 in the range of 10-20 μM. N8 treatment also reduced cleaved IL-1β and caspase-1 p10 protein expression, although expression of NLRP3 complex components (NLRP3, ASC, pro-IL-1β and pro-caspase-1) was not affected. Attenuation of pyroptosis was also observed in the presence of this compound. Similar results were obtained in bone marrow derived macrophages. Thus, dehydrohispanolone derivative N8 is postulated as a promising potent NLRP3 inflammasome inhibitor.

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