Abstract

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Sesquiterpene lactones of plant origin such as thapsigargin (TG) and trilobolide (TB) are potent inhibitors of sarco/endoplasmic Ca^{2+}-ATPase (SERCA), enhancing thus concentration of intracellular calcium. TG has been found to exhibit prospective immunotherapeutic properties. It inhibits growth of slowly proliferating and non-proliferating cells, and inhibits replication of viruses. The aim of present work was to investigate immunomodulatory potential of these compounds and compounds chemically different from sesquiterpene lactone TG, i.e. clotrimazole, artemisinin, dihydroartemisinin, curcumin. All these drugs are related to SERCA inhibition. The effects were analyzed in cultures of rat and mouse resident peritoneal cells. Production of nitric oxide (NO) by animal macrophages was assayed using the Griess reagent after 24hour´s culture. Supernatant levels of cytokines were determined by ELISA after 5-24hour´s of culture. The rat peritoneal macrophages produced high amounts of NO upon stimulation with TG and TB without any other immune stimulus (lipopolysaccharide) in comparison to other test SERCA inhibitors. The inhibitory effects of some drugs (curcumin, clotrimazole) on NO production are mainly due to their cytotoxicity. The compounds which are able to stimulate NO synthesis were able to induce secretion of cytokines (IFN-γ, TNF-α). Such potential was possessed by TG and TB. Production of NO remained unchanged in the presence of calcium chelating agents TMB-8 and the inhibitor of calcium release from sarco/endoplasmic reticulum dantrolen. It can be concluded that the immunostimulatory mode of action is structurally-related to sesquiterpene lactones and is unlikely the consequence of the intracellular calcium, which is enhanced by TG and TB.

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