Sigma-1 receptor antagonist BD-1063 attenuates Ca2+ responses induced by immunomodulators glutoxim and molixan in peritoneal macrophages

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Sigma-1 receptors are ubiquitous ligand-operated molecular chaperones in the endoplasmic reticulum membrane with a unique history, structure, and pharmacological profile. Acting as chaperones, sigma-1 receptors modulate a wide range of cellular processes in health and disease, including Ca^{2+} signaling processes. Disulfide-containing drugs glutoxim® (disodium salt of oxidized glutathione with d-metal at nanoconcentration) and molixan® (complex of glutoxim with nucleoside inosine) are used as broad-spectrum immunomodulators and cytoprotectors in the complex therapy of bacterial, viral and oncological diseases. Clinical studies have shown that molixan is effective in the prevention and treatment of COVID-19 infection; leads to a more rapid regression of the disease severity to a milder form. Earlier, we have shown for the first time that glutoxim and molixan cause biphasic intracellular Ca^{2+} concentration, $[Ca^{2+}]_i$, increase due to Ca^{2+} mobilization from thapsigargin-sensitive Ca^{2+} stores and subsequent store-operated Ca^{2+} entry in rat peritoneal macrophages. To elucidate the involvement of sigma-1 receptors in the effect of glutoxim and molixan on $[Ca^{2+}]_i$ in rat peritoneal macrophages and in regulation of Ca^{2+} signaling processes in macrophages in general, we used sigma-1 receptor selective antagonist, compound BD-1063 (1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine). Using Fura-2AM microfluorimetry we have shown for the first time that 20 mM BD-1063 significantly suppresses both Ca^{2+} mobilization (by 50.8 ± 9.3%) from Ca^{2+} stores and subsequent store-operated Ca^{2+} entry (by 54.0 ± 10.1%), induced by 100 mg/ml glutoxim or molixan in rat peritoneal macrophages. The data obtained indicate the involvement of sigma-1 receptors in the complex signaling cascade triggered by glutoxim or molixan and leading to $[Ca^{2+}]_i$ increase in macrophages. The results also suggest the involvement of sigma-1 receptors in the regulation of store-operated Ca^{2+} entry in macrophages.

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