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Sigma-1 Receptor Ligands Chlorpromazine and Trifluoperazine Attenuate Ca^{2+} Responses in Rat Peritoneal Macrophages

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Sigma-1 receptors are ubiquitous multifunctional ligand-operated molecular chaperones in the endoplasmic reticulum membrane with a unique history, structure, and pharmacological profile. Sigma-1 receptors bind ligands of different chemical structure and pharmacological effect and modulate a wide range of cellular processes in health and disease, including Ca^{2+} signaling processes. To elucidate the involvement of sigma-1 receptors in Ca^{2+} signaling processes in macrophages, the effect of sigma-1 receptor ligands, phenothiazine neuroleptics chlorpromazine and trifluoperazine, on Ca^{2+} responses induced by endoplasmic Ca^{2+}-ATPase inhibitors thapsigargin and cyclopiazonic acid, as well as by disulfide-containing immunomodulators glutoxim and molixan, was investigated in rat peritoneal macrophages. Using Fura-2AM microfluorimetry we have shown for the first time that chlorpromazine and trifluoperazine suppress both phases of Ca^{2+} responses induced by glutoxim, molixan, thapsigargin and cyclopiazonic acid. The data obtained indicate the involvement of sigma-1 receptors in the complex signaling cascade triggered by glutoxim or molixan and leading to intracellular Ca^{2+} concentration increase in macrophages. The results also suggest the involvement of sigma-1 receptors in the regulation of store-dependent Ca^{2+} entry in macrophages.

Keywords: trifluoperazine, chlorpromazine, sigma-1 receptors, peritoneal macrophages, intracellular Ca^{2+} concentration