J Clin Exp Tox, Volume 3
DOI: 10.4066/2630-4570-C1-006

Anti-allergic cromones exert its mechanism of pharmacological actions by inducing the release of Annexin A1

Sinniah A
University of Malaya, Malaysia

Anti-allergic cromones are well recognised as 'mast cell stabilizers' which prevent mast cell degranulation upon stimulation. Many studies have also reported that disodium cromoglycate and nedocromil, which are exemplars of cromones, can influence the other facets of inflammatory cascade including inactivation of polymorphonuclear leukocytes, inhibition of cytokine and eicosanoid release and chloride channel blockade. However, the exact mechanism underlying these effects remained a conundrum until recently. Our work now points to a mechanism involving the endogenous anti-inflammatory protein, Annexin (Anx) A1. The synthesis and secretion of this protein is regulated by glucocorticoids and mediates their action in many models of acute and chronic inflammation. We have therefore investigated the possibility that cromones control mast cell homeostasis and degranulation by promoting the release of Anx-A1 (abundant in mast cells). Cultured cord blood derived mast cells (CDMCs) and bone marrow-derived murine mast cells (BMDMCs) from wild type or Anx-A1-/- mice were pre-treated with nedocromil (0.5-10nM) for 5 min prior to 10 min stimulation with compound 48/80 (10µg/ml) to trigger degranulation. PKC activation is crucial for Anx-A1 externalization in CDMCs and nedocromil-induced Anx-A1 phosphorylation/externalisation was blocked by the PKC inhibitor Gö-6983 (10µM). Pre-treatment with nedocromil significantly ($p<0.05$) inhibited the release of histamine, PGD2, tryptase and β-hexosaminidase, however the drug was inactive in the presence of anti-Anx-A1 neutralising antibodys. The prospect that FPR2, the receptor for Anx-A1, might be involved in the acute actions of nedocromil was tested using the FPR2 antagonist (10µM) or in BMDMCs from fpr2/3-/- mice. Nedocromil was then unable to prevent PGD2 release in either model. However its action on histamine release does not seem to exclusively depend on FPR2, hence might involve another member of the FPR family. These findings indicate a novel paradigm by which Anx-A1 mediates the pharmacological actions of cromones as inhibitors of mast cell degranulation.

e: ajantha.sinniah@um.edu.my

Notes: