SODIUM SALICYLATE PREVENTS HYALURONAN ACCUMULATION IN TYPE B SYNOVIOCYTES BY BLOCKING CYCLOOXYGENASE ACTIVITY AND NOT BY SUPPRESSING NF-kB TRANSLOCATION

KM. Stuhlmeier, C. Pollaschek, and H. Bröll

Ludwig Boltzman Institute for Rheumatology, Kurbadstrasse 10, 1100 Vienna, Austria

Rheumatoid arthritis (RA) affects innumerable individuals. Little is know about the etiology of this debilitating disease. Despite the advent of a series of modern drugs for the treatment of RA, none-steroidal anti-inflammatory drugs such as salicylate are still a staple in the management of RA. There is sufficient evidence that hyaluronan (HA) can provoke all classical signs of RA. We tested the effect of sodium salicylate on HA accumulation/release in type B synoviocytes (FLS) and found that this substance can inhibit HA release induced by a series of proinflammatory stimuli. Here we report on the outcome of experiments investigating the mechanism of this inhibition. A series of studies have demonstrated that salicylate causes anti-inflammatory and anti-proliferative effects through the inhibition of nuclear factor-kappa-B (NF-kB). Most, if not all pro-inflammatory genes depend on the activation of this factor. We tested whether NF-kB activation is essential for the activation of HAS1 and whether inhibition of NF-kB translocation by salicylate accounts for the observed down-regulation of HAS1. Treatment of FLS with IL-1 results in approximately 50-fold induction of HAS1 mRNA. Electrophoretic-mobility-shift-experiments (EMSA) demonstrate that in FLS, IL-1 induces NF-kB translocation, an event preceded by phosphorylation and degradation of the inhibitor-kappa-B (IkB). We further demonstrate that the IL-1 effect on HAS1 accumulation is completely blocked by PDTC, a known inhibitor of NF-kB activation. Like PDTC, salicylate also blocks IL-1 induced HAS1 accumulation in a dose dependent manner. Interestingly, while PDTC completely blocked IL-1 induced translocation of NF-kB, salicylate had no effect, neither on IL-1 induced IkBa phosphorylation/degradation nor on NF-kB translocation. The EMSA data clearly exclude salicylate mediated NF-kB inhibition as the mode of action with regard to suppression of IL-1 induced HAS1 activation. Taken together, these data support the concept that salicylate prevents IL-1 induced HA accumulation through its effects on cyclooxygenase activity.