Suppression of NF-kappaB activity by sulfasalazine is mediated by direct inhibition of IkappaB kinases alpha and beta.


Source
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Abstract

BACKGROUND & AIMS:
Activation of NF-kappaB/Rel has been implicated in the pathogenesis of inflammatory bowel disease (IBD). Various drugs used in the treatment of IBD, such as glucocorticoids, 5-aminosalicylic acid, and sulfasalazine, interfere with NF-kappaB/Rel signaling. The aim of this study was to define the molecular mechanism by which sulfasalazine inhibits NF-kappaB activation.

METHODS:
The effects of sulfasalazine and its moieties on NF-kappaB signaling were evaluated using electromobility shift, transfection, and immune complex kinase assays. The direct effect of sulfasalazine on IkappaB kinase (IKK) activity was investigated using purified recombinant IKK-alpha and -beta proteins.

RESULTS:
NF-kappaB/Rel activity induced by tumor necrosis factor alpha, 12-O-tetradecanoylphorbol-13-acetate, or overexpression of NF-kappaB-inducing kinase, IKK-alpha, IKK-beta, or constitutively active IKK-alpha and IKK-beta mutants was inhibited dose dependently by sulfasalazine. Sulfasalazine inhibited tumor necrosis factor alpha-induced activation of endogenous IKK in Jurkat T cells and SW620 colon cells, as well as the catalytic activity of purified IKK-alpha and IKK-beta in vitro. In contrast, the moieties of sulfasalazine, 5-aminosalicylic acid, and sulfapyridine or 4-aminosalicylic acid had no effect. Activation of extracellular signal-related kinase (ERK) 1 and 2, c-Jun-N-terminal kinase (JNK) 1, and p38 was unaffected by sulfasalazine. The decrease in substrate phosphorylation by IKK-alpha and -beta is associated with a decrease in autophosphorylation of IKKs and can be antagonized by excess adenosine triphosphate.

CONCLUSIONS:

These data identify sulfasalazine as a direct inhibitor of IKK-alpha and -beta by antagonizing adenosine triphosphate binding. The suppression of NF-kappaB activation by inhibition of the IKKs contributes to the well-known anti-inflammatory and immunosuppressive effects of sulfasalazine.

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