Regulation of the histamine signaling pathway by inducible transcription factors: A novel mechanism for the anti-allergic actions of DSCG

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Histidine decarboxylase (HDC), by which histamine is formed from histidine in tissues, and H_1-receptors, which are activated by histamine, play a central role in the pathophysiology of allergic diseases. However, these transcription regulatory mechanisms are poorly understood. We have found that HDC expression is increased in different tissues after the animals were rendered endotoxemic by lipopolysaccharide, which can be suppressed by transfection of NF-κB decoy oligonucleotide, suggesting a crucial role of NF-κB activation in induction of HDC expression. On the other hand, we have provided evidence of up-regulation of H_1-receptors in tissues during endotoxemia, but other transcription factors such as AP-1, in addition to NF-κB, may participate in this gene expression, because only the blockage of NF-κB activation is insufficient to suppress superinduction of the H_1-receptor gene. Disodium cromoglicate (DSCG) is classified as an anti-allergy drug that is clinically effective for a variety of allergic diseases. While DSCG is known to inhibit chemical mediators from mast cells, many other mechanisms of actions of DSCG have been suggested. In mouse lung tissues, DSCG was found to inhibit sepsis-induced HDC overexpression, but its inhibition was incomplete even at the high dose. In contrast, the sepsis-induced increase in H_1-receptor expression was nearly completely eliminated by DSCG. This effect was possibly due to an AP-1 inhibition, since DSCG suppressed AP-1 activation even at the low dose and the high dose of DSCG was required for the inhibition of NF-κB activation. We suggest that DSCG may depress histamine synthesis and H_1-receptor gene expression due to the inactivation of inducible transcription factors, leading to anti-allergic and anti-inflammatory actions.