Pharmacologic Modulation of Th1 and Th2 Cell Subsets by Nedocromil Sodium

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Key Words

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The differentiation of T cells into Th2-like cells takes place under the influence of interleukin (IL)-4 [1] and tumor necrosis factor (TNF) [2]; and it has been suggested that cytokine release following mast cell activation may predispose this selection process in vivo [3, 4]. The effects of nedocromil sodium on mast cell activation are well documented [5], and studies assessing effects of the drug on IL-4 release from these cells are ongoing. Inhibition of TNF- α release from rat peritoneal mast cells by nedocromil sodium has been reported [6].

TNF- α is also released from Th1-like cells [2]. While the effects of nedocromil sodium on T cells have not been as well characterized as its effects on other proinflammatory cells, direct inhibitory effects have been shown on allergen- and mitogen-stimulated murine cells with Th1 characteristics. In these cells, inhibition of TNF- α production was observed at drug concentrations between 10^{-8} and 10^{-7} M [1].

In addition to activity on Th1-like cells, nedocromil sodium may act at the level of the B cell to down-regulate the ensuing inflammatory cascade. Kimata et al. [8] reported that nedocromil sodium (10^{-8} - 10^{-4} M) inhibited immunoglobulin production in normal human tonsillar B cells which had been up-regulated by exposure to *Staphylococcus aureus* Cowan strain I and IL-6, an effect which was blocked by preincubation of the cells with 100 U/ml IL-4. The mechanism involved is currently under investigation. However, it is interesting that nedocromil sodium (10^{-6} M) inhibited antigen-stimulated IL-6 production in alveolar macrophages isolated by bronchoalveolar lavage from allergic asthmatic patients [9]. IL-6, the cytokine used in the study by Kimata et al. [8] to stimulate B cells, also up-regulates T cell proliferation and IgE synthesis [9].

The question raised by these studies is whether nedocromil sodium, a pyranquinoline, can down-regulate IgE synthesis by altering T cell/B cell interactions. Cromolyn sodium, a

chromone, has been shown to inhibit T-cell-driven, IL-3-dependent IgE synthesis by human B cells through prevention of deletional switch recombination [10]. This is in contrast to glucocorticosteroids, which have been shown to enhance IL-4 production in murine T cell cultures [11] and to potentiate IL-4-induced IgE synthesis in several cell systems [12, 13]. Further studies with nedocromil sodium are being analyzed.

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