Role of Chloride Channel Modulation in the Mechanism of Action of Nedocromil Sodium

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Key Words

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Electrophysiological studies carried out by Penner et al. [1] have helped greatly in the understanding of the ionic events occurring in mast cells and have shown that stimulation of rat peritoneal mast cells with antigen results in the activation of chloride channels which allow chloride ions to enter the cells. This so-called delayed chloride current is responsible for maintaining activation of calcium channels which allow calcium ions to enter the cells and result in cell activation.

Recent studies by Romanin et al. [2] have demonstrated the ability of sodium cromoglycate to inhibit chloride ion channel activity in a mucosal-type mast cell line (RBL-2H3) detected by the patch clamp technique and this activity correlated with the ability of the compound to inhibit mediator (serotonin) release from the cells. The present studies were designed to evaluate further the ability of the chromones to modulate a chloride channel, probably involved in cell volume regulation, in mouse 3T3 fibroblasts. This channel may be identical to a previously reported chloride channel which was characterised following expression cloning using MDCK epithelial cells as the source of mRNA [3]. The channel was characterised as outwardly rectifying, calcium insensitive and blocked by nucleotides and was defined therefore as the ICln channel.

Electrophysiological recordings of chloride current were carried out in mouse 3T3 fibroblasts using a two-electrode voltage clamp. Voltage steps (800 ms) were made from -80 to +40 mV, and current amplitude were measured 50 ms after stepping to the different voltages. Both nedocromil sodium and sodium cromoglycate blocked the ICln after a voltage clamp step to +40 mV. Nedocromil sodium was more efficacious and more potent than sodium cromoglycate at blocking this current.

The present findings show both sodium cromoglycate and nedocromil sodium to inhibit hypotonic-saline-induced activation of a chloride channel in mouse 3T3 fibroblasts. It is interesting that the ICln channel is blocked by nucleotides, with cGMP the most efficacious [3]. Studies on rat peritoneal mast cells have shown cGMP to inhibit immunological activation, and a cross-tachyphylaxis exists between this agent and sodium cromoglycate [4]. Further studies are

required to determine whether nedocromil sodium and sodium cromoglycate inhibit chloride channel activity in inflammatory cells such as lung mast cells and eosinophils and whether this can be correlated with the inhibitory effects of the compounds on cell activation.

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