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Review article

Thimerosal
A versatile sulfhydryl reagent, calcium mobilizer, and cell function-modulating agent

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Abstract

An overview of the literature concerning the effects of thimerosal is presented. Because of its antibacterial effect, thimerosal is used for a variety of practical purposes such as antiseptic and preservative. In biomedical studies, thimerosal is used as a sulfhydryl reagent, and as a calcium-mobilizing agent. The ability of thimerosal to act as a sulfhydryl group is related to the presence of mercury. Relatively little study has been devoted to the mechanism of the reaction of thimerosal with the sulfhydryl group; the sulfhydryl reactive capacity is mostly concluded on the basis of inactivation of the effect by dithiothreitol (DTT). Thimerosal causes a release of calcium from intracellular stores in many cells types; this is followed by an influx of extracellular calcium. Both InsP3- and ryanodine-sensitive calcium stores may be affected. Studies with permeabilized cells or organelles show that the effect of thimerosal on calcium is dependent on the concentration: low concentrations of thimerosal stimulate calcium release, high concentrations are inhibitory. This dependence is not found in intact cells. Thimerosal may activate or inhibit a number of cell functions. These are often related to the ability to release calcium or with the sulfhydryl reactivity. In platelets, thimerosal causes aggregation, increase of arachidonic acid metabolism, and exocytotic release of serotonin. In neutrophils, thimerosal causes, besides an increase of cytosolic free calcium, an increase of formyl-methionyl-leucyl-phenylalanine (fMLP)-activated leukotriene release, and a modulation of chemotactic migration and exocytosis. At low concentrations, thimerosal induces chemotactic migration of neutrophils, in the absence of other chemoattractants. The effect is also observed with thiosalicylic acid, indicating that the stimulation of migration was due to the thiosalicylic acid moiety of the thimerosal molecule. At higher concentrations, thimerosal causes inhibition of fMLP-activated migration. Low concentrations of thimerosal, but not of thiosalicylic acid, induced exocytotic enzyme release from neutrophils. High concentrations of thimerosal inhibited fMLP-activated exocytosis. The results point to an involvement of calcium mobilization and calcium influx of activation, and reaction with sulfhydryl groups for inhibition.

Keywords: Thimerosal; Calcium; Sulfhydryl group; Neutrophil; Chemotaxis; Exocytosis

Thimerosal—also named thiomersal, merthiolate or sodium ethylmercuri-thiosalicylate—is a water-soluble derivative of thiosalicylic acid, with antibacterial and antifungal properties. The two important parts of the molecule are the thiosalicylic acid moiety, and the possession of mercury coupled to sulfur (Fig. 1). These two parts determine most of the properties of thimerosal. The carboxylic group of thiosalicylic acid makes the compound water-soluble because at physiological pH the compound is present as a sodium salt. Thimerosal is able to penetrate the cell membrane; it enters the cell as the free acid which is formed in the equilibrium with the charged carboxylate form. As a consequence the rate of penetration of thimerosal is pH-dependent. The mercury atom gives the compound oxidative character. The relative importance of the mercury and the thiosalicylic acid part can be easily determined by comparing the effects of thimerosal with those of thiosalicylic acid.

Thimerosal has two main applications. One group of applications is of a practical nature, and is related with the antibacterial and antifungal effect of thimerosal. It is widely used as an antiseptic agent and as a preservative in topical medicaments, cleaning solutions for eye lenses, cosmetics, and vaccines. The other application is in the biomedical laboratory. In the latter case the chemical properties of thimerosal, notably its ability to react as a sulfhydryl reagent, are used to study basic mechanisms in cell physiology, especially calcium homeostasis and processes related to the effect on calcium.

The practical applications of thimerosal are accom-

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