THE METABOLIC ACTIVATION MECHANISMS OF AMINOPYRINE TO CAUSE ALLERGIC REACTION: THE FORMATION OF RUBAZOIC ACID AND METHYLRUBAZOIC ACID FROM 4-AMINOANTIPYRINE IN PRIMARY CULTURES OF HUMAN HEPATOCYTES

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It is generally believed that low molecular weight chemicals sensitize and elicit effectively to induce an immune response if they bind irreversibly to tissue macromolecules. In this respect, we studied the metabolic activation mechanism of aminopyrine (AP) that is known to cause the allergic reaction. The formation of rubazoic acid (RA) and methylrubazoic acid (MRA) from AP and 4-aminoantipyrine (4-AA) in vivo were remarkably increased by the pretreatment of rats with 3-methylcholanthrene. Furthermore, 4-amino-1, 2-dihydro-5-methyl-2-phenyl-3-H-pyrazol-3-one (ADMP) which is the third-demethylation metabolite of AP produced RA using horseradish peroxidase and hydroperoxide or by autooxidation. ADMP bound to glutathione and isoeugenol both of which are free radical scavengers. When ADMP is injected into guinea pig skin, erythema was elicited in the skin as the delayed type hypersensitivity. These results strongly suggested that ADMP is one of haptens in AP allergy. It was further confirmed that the secretion of IL -10 increased with the culture medium of lymphocytes obtained from the treated rat spleen in ADMP. In this time, we clarified that the formation of RA or MRA occurred via ADMP from 4-AA using primary cultures of human hepatocytes. Furthermore, when IL-6 is added to the culture medium, the decrease in formation of RA and MRA was recognized. In contrast, when IL-10 is added to the culture medium, the increase in that was recognized. These findings suggest that IL-10 induced CYP enzymes contributing to the formation of ADMP directly.