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Role of metabolism by flavin-containing monooxygenase in thioacetamide-induced immunosuppression

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Thioacetamide has been known to cause immune suppression. In this report we studied the role of metabolic activation by flavin-containing monooxygenase in the thioacetamide-induced immune response. To determine whether the metabolites of thioacetamide produced by flavin-containing monooxygenase result in the immunosuppression, methimazole, a flavin-containing monooxygenase inhibitor, was used to block the flavin-containing monooxygenase pathway. Antibody forming cell response measured in BALB/c mice sensitized with sheep red blood cells was compared between the groups treated with thioacetamide in the presence or absence of methimazole pretreament. The pretreatment abolished the decrease of antibody forming cell number observed in the mice treated with thioacetamide alone. Spleen cell proliferation induced with either LPS or Con A was also decreased by thioacetamide in a dose-dependent manner. Spleen cells were exposed to thioacetamide with a drug-metabolizing system, liver microsome and NADPH, for 4 hrs prior to the stimulation with mitogen. The inhibitory effect of thioacetamide on cell growth was not detectable without the drug-metabolizing system and was diminished when coincubated with either SKF-525A, a cytochrome P-450 inhibitor, or methimazole. This reversion of cell growth was consistent with the result of IL-2 measurement that decreased production of IL-2 by thioacetamide was reversed by the pretreatment with SKF-525A or methimazole. In conclusion, thioacetamide-induced immunosuppression was at least in part due to the metabolites produced by flavin-containing monooxygenase as well as by cytochrome P-450.