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Studies on the metabolism of sulfametoxipirimidine in endotoxin tolerant mice

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IN A PREVIOUS paper[1] we demonstrated that the sulfametoxipirimidine is potentially toxic in endotoxin treated animals. We suggested that this phenomenon was due to the blockade of its various metabolical transformations and decreased urine elimination. Aware of the role of the spleen and liver in detoxification, we studied the metabolism of sulfametoxipirimidine in acute endotoxin toxemia and toxemia induced in endotoxin tolerant animals.

180 H strains of mice, males, weighing 18–22 g were divided into groups of 30 animals. The sulfametoxipirimidine was given orally in single doses of 100 mg/kg weight 1 hr after LD_{50} endotoxin. To

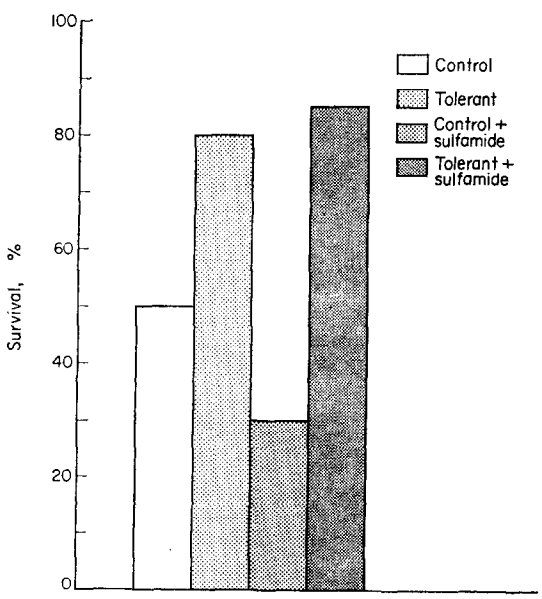

FIG. 1. Endotoxin induced toxicity in endotoxin tolerant and non-tolerant mice in association with sulfametoxipirimidine (30 mice for each series).

modify the functional capacity of RES, each animal was injected with endotoxin Salmonella typhi murium (Boivin type) i.v. in LD_{50} (0·1 mg/kg) for intact animals and for endotoxin tolerant animals (the tolerant animals was obtained by daily i.p. administration of endotoxin in increasing doses for 3 days: 0·025; 0·05 and 0·075 mg/kg). Four hr after sulfametoxipirimidine administration the mice were sacrificed by sectioning the art.carotidis and samples of liver and spleen were collected for estimation of sulfonamide. The amounts of free and bound sulfonamide was assayed by the Bratton–Marshall method.

The toxicity of endotoxin is lower in tolerant than in control mice. The sulfametoxipirimidine had no influence on the lethality in endotoxin tolerant animals (Fig. 1). Sulfametoxipirimidine increased the endotoxin lethality only in endotoxin non-tolerant mice. The amount of sulfametoxipirimidine in liver and spleen in non-endotoxin tolerant mice was lower than in control animals and its metabolism was abolished (Fig. 2). The amounts of sulfametoxipirimidine in endotoxin tolerant animals

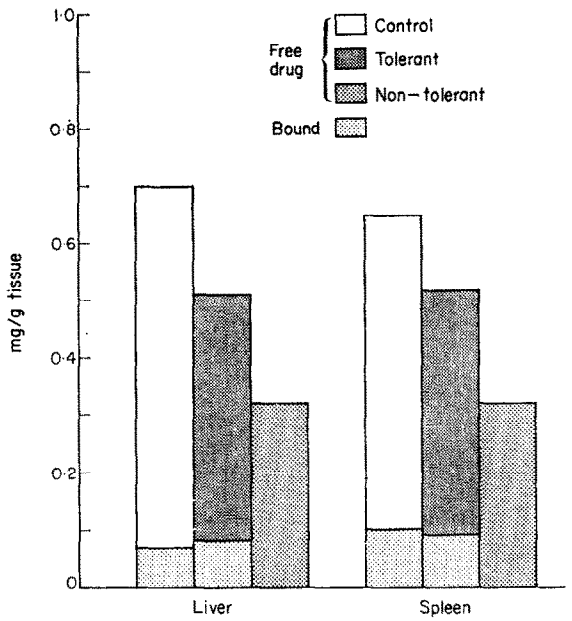

FIG. 2. Sulfametoxipirimidine level at 4 hr in liver and spleen in endotoxin tolerant and non-tolerant mice (30 mice for each series).

decreased but its metabolism in the liver and spleen was as in control animals. Our experimental findings demonstrate that the resistance of mice to endotoxin induced stress, depends on the metabolical activity of the spleen. Sulfametoxipirimidine is potentially toxic in endotoxin induced stress-toxemia—when the metabolical activity of the spleen is overloaded too by the presence of this drug.

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