Effect of malaria infection and endotoxin-induced fever on phenacetin O-deethylation by rat liver microsomes

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Abstract:

We have investigated the effect of malaria infection with the rodent parasite Plasmodium berghei and fever induced by Escherichia coli endotoxin on the metabolism of phenacetin to paracetamol by rat liver microsomes from young (4 weeks old) male Wistar rats (N = 5 in control and fever groups; N = 10 in malaria-infected group). Following determination of % parasitaemia, the malaria-infected group was divided into a low parasitaemia subgroup (N = 5; mean % parasitaemia = 9.87 +/- 2.6) and a high parasitaemia subgroup (N = 5; mean % parasitaemia = 36.6 +/- 8.1). The control group received normal saline. Total microsomal protein was not significantly affected by fever or malaria infection while cytochrome P450 levels were reduced by approximately 50% in the high parasitaemia subgroup, 20% in the low parasitaemia subgroup and 20% in the endotoxin-treated group. Phenacetin-O-deethylation kinetics were biphasic in both control and malaria-infected rats, but monophasic in endotoxin-treated rats. Total apparent intrinsic clearance (CL(int),total; calculated as Vmax/Km; Vmax is maximum velocity, Km is Michaelis constant) of phenacetin was reduced approximately 6-fold in low parasitaemia, 30-fold in high parasitaemia and 35-fold in fever. There was a poor correlation between CL(int),total and % parasitaemia (r = -0.6). However, log CL(int),total correlated inversely with % parasitaemia (r = -0.9), suggesting that Cl(int),total decreased exponentially with an increase in % parasitaemia. Phenacetin O-deethylation is a marker for cytochrome P4501A2 activity and the results of the present study suggest that both malaria infection and fever might specifically reduce P4501A2 activity in the rat.