Metabolism of Diazepam and Ethosuximide in rats with malaria and endotoxin-induced fever

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Abstract:

We have investigated the effects of malaria infection with rodent parasite Plasmodium berghei and fever induced by Escherischia coli endotoxin on the metabolism of diazepam to temazepam by rat liver microsomes, and on the clearance of ethosuximide in vivo in the rat. Livers from malaria-infected (parasitaemia =36.8+/- 7.6% endotoxin-treated or saline-treated (control) rats (N=5 per treatment) were used to prepare microsomes. These were incubated with diazepam (10-600ū M) for 10 minutes in an NADPH-generating system. V(max), K(m) and the intrinsic clearance V(max)/K(m) for the production of temazepam were determined. In separate experiments, ethosuximide (5mg/kg) was administered via the tail vein to control, malaria-infected and endotoxin-treated rats (parasitaemia=43.8+/- 5 %) under light ether anesthesia (N=5 per treatment). Total clearance of ethosuximmide was estimated form a single blood sample obtained 24h after drug administration. Diazepam metabolism was not affected by malaria infection or fever (V(max):1.31+/- 0.34,0.73+/- 0.27 and 1.07+/- 0.78 nmol/min/mg protein; K(m): 158.7 +/- 63.7, 175.3+/- 44.9 and 190.0+/- 81.8ūM; Intrinsic clearance/whole liver: 0.31+/- 0.16, 0.26+/- 0.1 and 0.29+/- 0.1ml/min in livers from control, malaria-infected and endotoxin-treated rats respectively; P>0.05). Similarly, clearance of ethosuximide in vivo was not affected by malaria infection or fever (1.3+/- 0.2, 1.3+/- 0.01 and 1.4+/- 0.4 ml/min/kg in control, malaria-infected and endotoxin-treated rats respectively; p>0.05). These results suggest that malaria infection and fever have no effect on the activities of the CYP3A isozymes thought to be involved in the metabolism of diazepam and ethosuximide