THE FATE AND ACUTE TOXICITY OF AFLATOXIN B1 IN THE MASTOMYS AND RAT

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The susceptibility to the toxic and carcinogenic effects of aflatoxin varies among species, the hamster and mouse being resistant compared with other animals. Species differences in susceptibility have been studied in relation to the processes of the metabolic activation and detoxification of aflatoxin in the liver. There has been accumulating evidence showing that the formation of AFB1-epoxide is critical for the biological action of AFB1 in susceptible species. However, GSTs-transferases to inactivate AFB1-epoxide has been shown to correlate well with the difference in susceptibility to AFB1 among mice, hamsters, rats, quails and guinea pigs. This suggests that major determinant of species differences in susceptibility to the effects of AFB1 is GST-catalyzed detoxification.

We have previously shown in an in vitro study that the cytosolic activity inhibiting the microsome-mediated AFB1-DNA binding in the presence of glutathione is higher in the liver of mastomys (praomys coucha), an african rodent, than in the liver of rats. In light of the close correlation between species susceptibility and cytosolic GST activity in several species, the mastomys may be resistant to AFB1, but its susceptibility is unclear. In order to clarify the relative susceptibility of the mastomys to the toxic effects of AFB1, we studied the fate and acute toxicity of AFB1 in the mastomys in comparison with those in rats.

The amount of [3H] excreted in the feces within 72 hrs after the oral administration of [3H]AFB1 was greater in the mastomys than in the rats. The tissue levels of [3H] expressed per gm wet weight were higher in the rats than in the mastomys in all the organs examined and in the plasma and blood cells. In the rats, the highest level was noted in the liver, followed by the kidneys and plasma. The AFB1-DNA level of the pooled liver (n=3) was 0.0074 and 0.0005 ng equivalent of AFB1/mg DNA in the rats and mastomys, respectively.

IV-injected [3H]AFB1 showed that the [3H] level was 4-9 fold higher in the liver than in the other tissues in the rats while the [3H] level was similar in all the tissues in the mastomys. The [3H] level of the liver was markedly higher in the rats than in the mastomys, while there were no marked differences in the level of the other tissues between the two species (Fig.3). The amounts of [3H] in the intestines and feces of the rats and mastomys were 140±53.9 ng equivalent of AFB1 (n=2) and 143.4±1 4.6 ng equivalent of AFB1 (n=2), respectively, the values being equivalent to 20% and 45%, respectively, of the injected dose.

The AFB1-DNA level of the liver was 0.29±0.035 (n=2) and 0.01±0.0060 (n=2) ng equivalent of AFB1/mg DNA in the rats and mastomys, respectively.

Toxic effects of AFB1

In the rats, the liver was severely affected. At the light microscopic level, the focal degeneration of hepatocytes with an eosinophilic cytoplasm and pyknotic nucleus was observed. The lobules were more extensively affected in the rats treated with the higher dose (2.0 mg/kg). In the interlobular connective tissues, the perivascular infiltration of leukocytes and occasional disarrangement of the bile duct epithelium were noted. The electron microscopic observation of the hepatocytes revealed some cytological changes characteristic of necrotic degeneration: chromatina margination of the nucleus, dilatation of the endoplasmic reticulum, and mitochondrial swelling.

In contrast, the mastomys showed very few pathological lesions in the liver or the kidneys. In the two mastomys treated with 10 mg/kg AFB1, there was a small white area in the liver where hepatocytes deposited excessive glycogen around the nucleus. However, since the lesion was extremely focal and clear-bounded, whether this was a direct consequence of the AFB1 treatment remains unclear. The mastomys strain we used was affected by inherited lipid storage in the hepatocytes, but the nucleus and other organelles were normal at both the light and electron microscopic levels irrespective of whether they were treated with AFB1.

The results of the fate of [3H]AFB1 demonstrate that AFB1 and/or its metabolites distribute almost evenly in various tissues and are eliminated rapidly in the mastomys whereas they are accumulated mainly in the liver and eliminated slowly in the rat. Such differences may in large part reflect the difference between the two species in the levels of AFB1 bound to macromolecules including DNA in the liver, because the levels of AFB1-DNA in the liver were much higher in the rats than in the mastomys. The results of the toxic effects of AFB1 demonstrate clearly that the mastomys is far more resistant than the rat.

Taken together, the relative susceptibilities of the rat and mastomys indicate that the GST activity toward exo-epoxide correlates well with the susceptibility to the acute toxicity of AFB1 in these species.

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