The fate of aflatoxin B₁ in animals

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Summary

The study of the fate of aflatoxin B₁ (AFB₁) in the rat demonstrated that the main site for the toxin absorption is the small intestine. AFB₁ transferred from the intestinal lumen almost exclusively into the mesenteric blood. The increase in the rate of absorption nearly in proportion to the increase in AFB₁ concentration in the medium suggests that AFB₁ is absorbed substantially by passive diffusion. After being absorbed from the intestine, AFB₁ enters exclusively into mesenteric vein and is partially converted to AFL by the blood cell. Comparison of the liver microsomal activity forming AFB₁-DNA adduct among various species showed no correlation between the activity and species difference in susceptibility to AFB₁ toxicity. However, a reverse relationship was observed between the liver cytosol glutathione-S transferase (GST) activity and species susceptibility, but no relationship was noted between the liver cytosol aldehyde reductase activity toward AFB₁ aldehyde activity and species susceptibility. The results indicated the importance of liver cytosol GST activity in species differences in susceptibility to AFB₁.

Key words : aflatoxin B₁, glutathione-S transferase, aldehyde reductase, species difference

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This review summarizes our studies on the fate of aflatoxin in animal body including aflatoxin B₁ (AFB₁) metabolism in relation to species differences in susceptibility to AFB₁ toxicity and carcinogenicity. These studies presented new aspects of the fate of aflatoxin in animal body when they were published between 1983-2005 in relating journals and book^{4, 18-22)}.

1. The fate of AFB₁ from the gastrointestinal tract to blood circulation

In order to delineate the fate of AFB₁ in animal body, a series of experiments were performed using rats. Whether AFB₁ is absorbed from the stomach or the small intestine was investigated by injecting [3H]-AFB₁ directly into either lumen of the rat under pentobarbital anesthesia. After the abdomen was opened, the proximal end of duodenum was ligated, and 1.0 mL saline containing 3H-AFB₁ was injected into the lumen of the stomach or proximal jejunum with a syringe. Bile was collected for 30 min through a polyethylene tube inserted into the common bile duct. Radioactivity which appeared in bile was remarkably higher when AFB₁ was given in the small intestine than in the stomach. (stomach, 1.47 +/- 1.47

ng equivalent of AFB₁ per 30 min; small intestine, 41.7 +/-10.3 ng equivalent of AFB₁ per 30 min).

In the next series of experiment, intestinal sites were compared for AFB₁ absorption. After the abdomen was opened under pentobarbital anesthesia, small cuts were made at the proximal and distal sites of the 11- to 18-cm segment of the duodenum, proximal jejunum, or ileum. An inflow tube connected to a peristaltic pump and an outflow tube were inserted into the proximal and distal openings, respectively, both being secured by ligatures around the intestine. The perfusion medium was recirculated at a speed of 0.76 or 3.1 mL/min for 60 min through the two tubes and the segment. In addition to [3H]AFB₁ or aflatoxin G₁ (AFG₁), [14C] polyethylene glucol was contained in the perfusion medium to determine the change in volume of the medium during perfusion. The rate of disappearance of the aflatoxins from the medium was calculated from the initial and final concentrations of [3H]AFB₁, AFG₁, and [14C]PEG. Also [3H] appeared in bile was determined.

The result showed that the rate of disappearance of AFB₁ from the perfusion medium, was the highest in the duodenum, and nearly the same in the jejunum and ileum, increasing in proportion to the increase in AFB₁ concentration in the medium in either site. The same tendency was observed in biliary excretion of [3H] (Table 1). The rate of AFG₁, when the duodenum was perfused, was significantly lower than the rate of AFB₁.

Route of absorption was studied by determining the appearance of AFB₁ and aflatoxinol (AFL) in both the lymph and the venous plasma. The appearance was studied by examining the appearance of AFB₁ and AFL in both fluids during perfusion of the jejunum with medium containing AFB₁. Inflow and outflow tubes were inserted into the segment as described above. Mesenteric venous blood draining only from the perfused segment of the jejunum and mesenteric lymph were collected at 20-min intervals¹⁾. AFB₁ and AFL were detected in the 20-min collected plasma (AFB₁, 0.22+/-0.07 µg/ml; AFL, 0.05+/-0.19 µg/mL) but not in the 20-min collected lymph (AFB₁ could not be visualized; AFL, lower than 0.025 pg/mL).

Metabolic degradation of AFB₁ during absorption was studied by determining the distribution of radioactivity contained in chloroform extracts of the venous plasma and intestinal perfusate on TLC. The medium containing [3H]AFB₁ was recirculated at a speed of 0.76 mL/min for 20 min through a segment made at the duodenum, proximal jejunum, or ileum, during which the mesenteric venous blood draining from the segment and mesenteric lymph were collected. When the duodenum or jejunum was

Table 1. Rate of biliary secretion of ³H in rats of intestinal perfusion

Initial concentration of AFB ₁ in perfusion medium (µg/mL)	Perfusion site	Rate of ³ H secretion (µg equivalent of AFB ₁ /g/hr)
1.0	Duodenum	3.57±0.66
1.0	Jejunum	1.05±0.23*
1.0	Ileum	1.10±0.10*
4.0	Duodenum	9.83±0.93
4.0	Jejunum	5.15±0.46*
4.0	Ileum	7.36±0.78

Note. Numbers of rats used were three to seven for each group.

*Significantly different from the value of duodenum.

p < 0.05, Student's *t* test.

perfused with the medium containing a low concentration of AFB₁ (10 ng/mL), more than 20 % of the radioactivity in the plasma extracts distributed in the regions other than those of AFB₁ and AFL on TLC. However, when the ileum was perfused under the same condition or when the jejunum or ileum was perfused with a high concentration of AFB₁ (1 µg/mL), radioactivity distributed almost exclusively in the regions of AFB₁ and AFL. Radioactivity in the perfusate extracts was mostly in the region of AFB₁.

For studying AFB₁ absorption in different ages and reproductive stages, two or three segments were made at various sites of the small intestine in each rat and connected to separate reservoirs through inflow and outflow tubes under anesthesia. The medium containing AFB₁, [3H]AFB₁, and [14C]PEG was recirculated through each segment. The perfusion speed was set at 0.58 to 1.40 mL/min, so that it was nearly proportional to the internal circumference of the intestinal duct. A drastic change in the rate of disappearance of AFB₁ from the intestinal perfusate was noted from suckling to post weaning period. In suckling rats, the rate was much higher than that in adult or post weaning rats (Table 2). In female rats, the rate was higher in duodenum than in jejunum in diestrous rats, while it was similar in various sites in lactating rats (Table 2).

The results of this study demonstrated that the main site for the toxin absorption is the small intestine. Consistent with the observation in sheep²⁾, AFB₁ transferred from the intestinal lumen almost exclusively into the mesenteric blood. The increase in the rate of absorption nearly in proportion to the increase in AFB₁ concentration in the medium suggests that AFB₁ is absorbed substantially by passive diffusion. The lower rate of absorption of AFG₁ compared with that of AFB₁ suggests that lipid solubility of aflatoxin, and therefore its diffusional movement across the membranous structure lying between epithelial surface and blood capillary, is a determinant of aflatoxin absorption.

The metabolic activity of the intestinal mucosa and its importance in the intestinal transfer has been shown for several exogenous compounds³⁾. Metabolic profile of AFB₁ in the mesenteric venous plasma during the process of its absorption on TLC showed that the proportion of radioactivity of the chloroform extracts of plasma from the jejunum was nearly the same as that noted in plasma of the blood incubated with AFB₁ *in vitro*⁴⁾, indicating that conversion of AFB₁ to water soluble metabolites can be neglected when it transfers across the intestinal wall. Radioactivity distributed mostly in the AFB₁ and AFL regions when the duodenum or jejunum was perfused with the medium containing a relatively high concentration of AFB₁. However, AFB₁ was apparently converted to other metabolites by the jejunal

Table 2. AFB₁ absorption in relation to age and reproductive stage

Age	Sex	Stage	AFB ₁ absorption (µg/g/hr)			Perfusion speed (mL/min)
			Duodenum	Jejunum	Ileum	
2.5 week	M ^a		96.5 ± 28.1	207.7 ± 40.5		0.58
4.5-5.0 week	M		14.2 ± 1.42*	6.96 ± 1.10* ^{**}		0.70
Adult	M		4.88 ± 0.57*	3.42 ± 0.59* ^{**}	3.53 ± 0.30	1.40
Adult	F ^a	D ^b	6.45 ± 1.55*	1.92 ± 0.82*	4.32 ± 0.30	1.40
Adult	F	L ^b	4.05 ± 0.39*	3.31 ± 0.19*	3.16 ± 0.53	1.40

^a M, male; F, female. Numbers of rats used were three to six in each group.

^b D, diestrus; L, Day 10 of lactation.

* Significantly different from the value of rats of 2.5 weeks. $p < 0.05$, Tukey test.

** Significantly different from the value of duodenum. $p < 0.05$, Tukey test.

and duodenal tissues, when they were perfused with a relatively low concentration of AFB₁. Most of the radioactivity of the extract of plasma from the ileum was found in the AFB₁ and AFL regions even when perfused with the low concentration of AFB₁. These results suggest that the metabolic degradation of AFB₁ by the duodenal and jejunal tissues cannot be neglected when luminal concentrations of AFB₁ are relatively low. No notable difference in metabolic activity between the duodenum and the jejunum suggests that such degradation of AFB₁ during its absorption is not involved in the mechanism of the differences in the rate of AFB₁ absorption among various sites of the small intestine.

The appearance of AFB₁ and AFL in the mesenteric venous blood from the perfused intestine raised the possibility that AFL was formed by blood but not by intestinal tissues. To gain insight into this, the blood from various animal species was incubated with AFB₁ or AFL at 37 °C, and were developed on TLC. Incubation of blood with AFB₁ or AFL showed marked inter-conversion of AFB₁ and AFL in the blood of rats, hamsters, mice, and Mongolian gerbils, but not in the blood of guinea pigs, rhesus monkeys, squirrel monkeys, or humans. Interconversion occurred in red blood cell suspensions but not in plasma, indicating that the red blood cells are responsible for AFB₁-AFL interconversion in the blood.

2. Transfer of AFB₁ from mother to fetus and suckling pups

Administration of AFB₁ to pregnant animals causes malformation, death and growth retardation in fetuses of hamsters, mice and rats⁵. When AFB₁ was given to female mice and rats during gestation or lactation, their offspring show higher incidence of liver tumors than control animals^{6, 7}. However, biochemical processes involved in such effects of aflatoxin remain uncertain. To gain a better understanding of the effects of aflatoxin in fetal and suckling rats, we studied the metabolic activity of the liver during development and the transfer of (³H)-B₁ from pregnant and lactating rats to the liver of their offspring.

After ip injection of (³H)-AFB₁ dissolved in DMSO or AFB₁ dissolved in corn oil to rats, tissue samples were taken from them under light ether anesthesia. Fetal blood was taken from the umbilical vein through a polyethylene tube inserted into it, and amniotic fluids from the amniotic cavity by a syringe. For studying sub-cellular distribution of (³H) and metabolic activity of the liver, livers of adult rats were removed after perfusion with cold saline, and those of fetuses and suckling rats were cut into pieces and washed briefly after being removed. Milk was collected from the stomach of suckling rats.

Glutathione S-transferase (GST) activity in the liver cytosol was determined using 2,4-dinitrochlorobenzene as a substrate. Microsomal activity to bind AFB₁ to DNA was determined by incubating calf thymus DNA and (³H)-AFB₁ with the microsomes. To determine tissue and milk radioactivity, protein recovered from phenol layer of the tissue homogenates, and milk from the rat stomach, were combusted in an Oxidizer to dissolve (³H) into scintillation medium. The other samples were mixed with Atomlight without pre-treatment. Radioactivity was determined in a scintillation counter.

Microsomal activity to bind AFB₁ to DNA increased from fetal age to 9 days of age. The activity on 9 and 12 days of age was similar to that in adult male rats, when expressed on the basis of amount of microsomal protein, GST activity of liver cytosol remained nearly constant until 12 days of age. The levels were 1/2-1/3 of those in adult male rats.

The serum concentration of (3H) decreased rapidly in the pregnant and male rats during the 72 hrs after (3H)-AFB₁ administration, whereas the (3H) concentration in fetal serum was almost unchanged during the first 24 hrs and then decreased slowly compared to the maternal serum concentration. Concentration of (3H) in amniotic fluid, were similar to, or slightly higher than those in fetal serum. When mother rats were given (3H)-AFB₁ on day 0 of lactation, serum concentrations of (3H) in suckling rats increased gradually to the fetal level by day 4. Detectable amounts of (3H) was contained in milk taken from the stomach of the suckling rats (29-266 pmole equivalent AFB₁/g).

(3H) contents in the liver of fetuses and suckling rats remained relatively constant. (3H) was also detected in hepatic macromolecules from offspring of mothers which were given (3H)-AFB₁ on day 19 of pregnancy or during lactation. The maximal level of DNA binding found in suckling rats was close to 1/5 of that in young adult male rats. The levels of (3H)-AFB₁ binding to hepatic macromolecules were far lower in the fetal and suckling rats than in the young adult male rats (Table 3). These results demonstrate clearly that aflatoxin binds to hepatic macromolecules of fetal and infant rats after transferring through the placenta and milk from their mothers.

Examination of metabolic activity of liver showed that hepatic microsomes' ability to bind AFB₁ to calf thymus DNA increased remarkably from fetal age to 9 days of age, while cytosolic GST activity remained nearly constant during those stages of rat growth.

Neonatal rats are known to be more sensitive to acute toxicity of AFB₁ than adult rats⁸⁾. Aflatoxin binding to hepatic macromolecules or protein has been postulated to play an important role in its acute toxicity⁹⁾. However, the low levels of aflatoxin binding to hepatic macromolecules in neonatal rats indicates that mechanisms other than covalent binding of aflatoxin to hepatic macromolecules may be involved in high toxicity of aflatoxin to these rats. One possible mechanism for it might be relatively high rate of AFB₁ absorption from the intestine of neonatal rats.

Table 3. The level of hepatic macromolecule-bound aflatoxin in fetal and suckling rats whose mothers were given [3H]AFB₁ (0.5 mg/kg) in comparison with that in mothers and male rats.

Time of [³ H]-B ₁	Time of sacrifice		pmoles aflatoxin bound/mg macromolecule (× 10 ³)		
			DNA	RNA	Protein
p 19 ^a	p 20-22	Fetus	16-30	15-160	6-11
		Mother	1056-5120	4384-6080	160-374
p 19	L 1-4	Suckling	31-99	80-1792	4-9
L 0 ^b	L 1-2	Suckling	80-1405	27-435	2-8
L 9	L 10-11	Suckling	566-886	141-378	13-16
D 0 ^c	D 1-3	Male 5wks	3206-6730	11221-26930	866-1603

^a, p 19 indicates day 19 of pregnancy (day 0=the day of mating).

^b, L 0 indicates 0 day of age of offspring.

^c, D 0 indicates the day of [³H]-B₁ administration.

3. Susceptibility of the mastomys to AFB₁

The relative susceptibility of mastomys (*Praomys coucha*) to the acute toxicity to AFB₁ was studied by comparing the toxic effects of a single gastric intubation of AFB₁ at a dose of 1.0, 2.0, 4.0 or 10.0

mg/kg in male mastomys and Fischer rats. The animals were killed 48 hr after AFB₁ administration, and their tissues and blood were taken for histopathology and blood biochemistry. The result showed marked microscopic changes in the liver of the rats given AFB₁ at a dose of 1.0 or 2.0 mg/kg, involving hepatic necrosis and proliferation of bile ducts. However, AFB₁ caused no marked pathological changes in the liver or kidney of the mastomys at any doses, except for minor changes in hepatic cells of a limited area at a dose of 10.0 mg/kg. The blood levels of the biochemical parameters GOT, GPT, LDH and TBI were extremely high in AFB₁-treated rats, but the levels of these parameters were within normal ranges in the AFB₁-treated mastomys (Fig. 1).

Furthermore, a single gastric intubation at a dose of 20.0 mg/kg did not cause the death of any of four mastomys, indicating the mastomys to be more resistant to the AFB₁ toxicity than the Fischer rat in which 1-2 mg/kg was estimated as the LD₅₀ value¹⁰.

To clarify the fate of AFB₁ in both the animals, they were given [3H]AFB₁ by gastric intubation at a dose of 1.0 mg/kg. After dosing, their urine and feces were collected for 72 hr, and blood was taken at 72 hr. The tissue and feces radioactivities were counted in a scintillation counter after the tissue was combusted in an oxidizer. The radioactivity retained in the liver was higher in the rat than in the mastomys. Feces were the main excretion route in both the species, the mastomys excreting [3H] more rapidly than the rat. The plasma levels of [3H] fell more rapidly in the mastomys than in the rat. These results demonstrated that AFB₁ and its metabolites distributed almost evenly in various tissues, and were eliminated rapidly in the mastomys, while they are accumulated mainly in the liver and eliminated relatively slowly in the rat. Such differences in the fate of AFB₁ may reflect the difference between the two species in the AFB₁ level bound to macromolecules in hepatic cells, because the determination of [3H] of DNA purified using a purification kit revealed the AFB₁-DNA level of the pooled liver to be 0.0074 and 0.0005 ng equivalent of AFB₁ per mg DNA in the rat and mastomys, respectively. This difference in the AFB₁-DNA level between the two species may directly reflect the difference in the level of AFB₁ epoxide capable of binding to cellular macromolecules directly or via AFB₁ dihydrodiol.

Fig. 1. Levels of blood clinical parameters at 48 hr after oral AFB₁. Left panel: Rat, Right panel: Mastomys.

4. GST activity toward AFB₁-epoxide in various species of animals

In order to characterize the liver GST activity toward AFB₁-epoxide in the mastomys in comparison with other rodent species, *in vitro* studies of the cytosolic GST activity toward AFB₁-epoxide and microsomal activity forming AFB₁-DNA adducts using mastomys, rat, mouse and hamster liver were performed.

For measurement of microsomal activity of the binding of AFB₁ to DNA, the microsomal fraction of the liver, [³H]AFB₁, calf thymus DNA, NADPH, G-6-P and G-6-P dehydrogenase were incubated at 37 °C, and then radioactivity of the DNA which was precipitated with ethanol from the incubation mixture was counted with a scintillation counter. The microsomal activity was higher in mastomys and hamsters than in mice and rats (Fig. 2). Since the rats used were male Fischer rats, which are susceptible to the acute toxicity and carcinogenicity of AFB₁, this result indicates that the species differences in susceptibility to AFB₁ do not reflect the species differences in the microsomal activity generating AFB₁-DNA adduct. No large differences were noted (Fig. 2) between the sexes in any species, indicating no contribution of the microsomal activity to the well known sex differences of AFB₁ toxicity and carcinogenicity.

Fig. 2. Microsome activity binding AFB₁ to DNA and cytosol activity toward AFB₁-epoxide.

The cytosol GST activity was measured by incubating liver cytosol fractions from various animals, hamster liver microsomes for generation of AFB₁-epoxide, [3H]AFB₁ and the same coenzymes as above. The reaction mixture was extracted with chloroform, and the remaining aqueous layer was loaded on a SepPak C18 column to obtain the AFB₁-DNA fraction. AFB₁-GSH in the fraction was determined by HPLC connected to a flow scintillation analyzer using 37 % methanol in 30 mM potassium phosphate buffer (pH4.0) as a mobile phase. AFB₁-GSH was identified according to the method of Holeski *et al*⁽¹¹⁾.

The GST activity toward AFB₁-epoxide was highest in mastomys liver, and higher in the hamster and mouse livers than in the rat liver. This difference in the activity among species is well correlated with species difference in susceptibility to AFB₁ toxicity, because the LD₅₀ values of the mastomys, mouse, hamster and rat are >20, 9.0, 10.2 and 1.0-2.0 mg/kg. Therefore, this result indicates the importance of the GST activity in determining species difference in susceptibility to AFB₁ toxicity. The GST activity was higher in the female than the male rats, indicating also the importance of GST in the sex difference of susceptibility to AFB₁ in rats.

5. The contribution of liver GST and aldehyde reductase activities to species susceptibility

To determine the liver GST activities toward AFB₁-epoxide, AFB₁ was incubated with GSH in the presence of liver cytosol from these animals and the amount of AFB₁-GSH formed was determined. The hamster liver microsomes were added to the reaction mixture to metabolize AFB₁ to AFB₁-8,9-epoxide. All the animal species possessed GST activities; the rate of AFB₁-GSH formation increased up to a maximum with the increase of the AFB₁ concentration according to the model of the first-order enzyme reaction kinetics. The V_{max} values of GST activities in rodent species were higher than those in the other species. The activity was high in the hamster, mouse, rat, trout and pig liver tissues, in this order, indicating a close relationship with species differences in susceptibility to the acute effect of AFB₁. A close relationship to the species susceptibility was also noted in the affinity constant expressed as the K_m value, which tended to be higher in the trout and pig than the rodent species.

The reductase toward AFB₁ has been regarded to contribute to detoxification of AFB₁ from the finding of modulation of AFB₁ toxicity or carcinogenicity by phase 2 enzyme inducers⁽⁷⁾. To determine the liver AFB₁-dialdehyde reductase in the above animal species, AFB₁-dialdehyde, which was synthesized from the AFB₁ exo epoxide according to the method of Guengerich *et al.*, was incubated in the presence of liver cytosol and the amount of AFB₁-dialcohol formed was determined by HPLC (a pirkele-concept chiral column packed with D-phenylglycine covalently bound to aminopropyl silica) using 37 % methanol in 30 mM potassium phosphate buffer (pH4.0) as a mobile phase. AFB₁-dialcohol synthesized from the AFB₁-exo epoxide according to the method of Guengerich *et al.*⁽¹²⁾ was used as a standard. The result (Table 4) showed that the liver cytosol of all the animals possessed the reductase activity. However, the lowest values of V_{max} and K_m were noted in the trout and relatively high values were in the pig, although both these species are more susceptible to AFB₁ than are the others.

The Lineweaver-Burk plot, which was prepared from data of this experiment, indicated that the velocity of the conjugation of AFB₁ to GSH was high in the order of the hamster, mouse, rat, pig and trout when the concentration of AFB₁ was lower than 1 µg/mL, the order being the same as that of the different susceptibilities. Such low levels of AFB₁ may mimic in vivo conditions, because the highest

Table 4. Comparison of GST and aldehyde reductase activities among animal species.

species	LD ₅₀ (mg/kg)	Glutathione transferase				Aldehyde reductase activity			
		V _{max} (pmol/mg protein per min)	K _m (μM)	V _{max} /K _m (μL/mg per min)	r ²	V _{max} (pmol/mg protein per min)	K _m (μM)	V _{max} /K _m (μL/mg per min)	r ²
Hamster	10.2	184.30±23.33	24.14±0.92	7.60±0.67	0.997	338.38±91.88	227.52±78.48	1.52±0.12	0.903
Mouse	9.0	84.19±19.84	30.38±5.65	2.74±0.14	0.938	233.32±16.66	248.16±83.88	1.03±0.28	0.977
Rat	1.0-2.0	34.44±6.19	17.43±6.15	2.11±0.39	0.982	>134.02±53.64	>225.98±64.04	—	0.994
Pig	0.62	9.84±3.62	50.93±36.56	0.29±0.13	0.975	346.42±56.12	194.18±69.28	1.92±0.39	0.921
Trout	0.81	13.98±7.81	109.04±71.57	0.14±0.02	0.997	34.68±6.12	6.30±5.5	19.57±16.12	0.885

The data were mean ± SE of three animals except for the trout (*n*=2). Substrates for GST and aldehyde reductase were AFB₁ and AFB₁ dialdehyde, respectively. Significant difference (*P* < 0.05) by Turkey's Kramer test: GST V_{max}: hamster vs rat, trout; rat vs trout. GST K_m: none. GST V_{max}/K_m ratio: hamster vs mouse, rat, pig, trout. Aldehyde reductase V_{max}: rat vs pig; rat vs hamster; mouse vs trout. Aldehyde reductase K_m: hamster vs trout. Aldehyde reductase V_{max}/K_m ratio: hamster vs mouse, pig, trout.

level of radioactivity in the blood serum had been noted to be equivalent of 0.9 μg/mL in rats given 0.6 mg radiolabelled AFB₁ per kg bw by Coulombe and Sharma¹³⁾. However, the velocity of reduction of AFB₁-dialdehyde to AFB₁-dialcohol was not related to species susceptibility.

Thus, the result of this study demonstrate that GST toward AFB₁, but not aldehyde reductase, is a determinant of the variation of species susceptibility, although possible contribution of the other factors such as epoxidase toward AFB₁ cannot be ruled out. AFB₁-GSH, whose formation depends on the GST activity, is water soluble and excreted efficiently in urine and bile¹⁴⁾. Therefore, the AFB₁-epoxide to AFB₁-GST conversion may compete with the formation of AFB₁-DNA adducts and AFB₁ dialdehyde, which binds to primary amine groups in protein via Schiff base reactions¹⁵⁾. Although hepatic aldehyde reductase can affect the binding of AFB₁-dialdehyde to cellular proteins, the contribution of AFB₁ aldehyde reductase to the inhibition of the toxic effects of AFB₁ might be far smaller than GST. This notion is consistent with a recent finding of Roebuck *et al.*¹⁶⁾ that liver-specific aldehyde reductase transgenic rats showed no change in their susceptibility to AFB₁, although their ability to form AFB₁ alcohol was enhanced.

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アフラトキシンB₁の生体内運命

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ラットを用いたアフラトキシンB₁ (AFB₁) の生体内挙動に関する研究によって、AFB₁の主な吸収部位が小腸であること、とくに十二指腸から効率よく吸収され、腸間膜静脈へ移行することが明らかにされた。移行中にアフラトキシコール (AFL) に変換されるが、これは血球による代謝を反映したものであった。各種動物の肝臓マイクロゾームのAFB₁-DNA結合活性 (AFB₁-エポキシド生成活性) を比較検討した結果、この活性は、AFB₁の毒性に対する感受性の動物種差との間に一定の関係をもたなかった。肝臓サイトゾールのアルデヒドリダクターゼ活性の動物種差も、AFB₁毒性に対する動物種差とは対応していなかった。しかし、肝臓サイトゾールのグルタチオンSトランスフェラーゼ (GST) 活性が強いほど、AFB₁毒性に対する感受性が低いという関係が認められたことから、このGST活性の相違がAFB₁毒性に対する動物種差を招来することが示唆された。

キーワード：アフラトキシンB₁, グルタチオンSトランスフェラーゼ, アルデヒドリダクターゼ,
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