Effect of Perfluorodecalin on Picrotoxin Toxicity and Some Detoxication Systems

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Preliminary administration (at least 7 days before the experiment) of perfluorodecalin boosts resistance to the toxic action of picrotoxin in rodents. The antidotal activity of diazepam rises under these conditions. Perfluorodecalin induces the activation of monooxygenase, conjugation, and antioxidant detoxication systems; the protein content increases in the blood serum and carboxylesterase activity is enchanced.

Key Words: *picrotoxin; perfluorodecalin; induction; detoxication systems; toxicity*

Preliminary administration of barbiturates to rodents has been reported to result in a decrease of the organophosphorus toxicity [8]. Benzonal and phenobarbital have been found to raise resistance to the toxic gamma-aminobutyric acid (GABA)-lytic action of picrotoxin and bicuculline when preinjected 3 times to mice [2]. The antidotal activity of diazepam was enhanced under these conditions. Perfluorocarbons are a new class of inductors of phenobarbital type [3,5]. A preliminary administration of fluorocarbon emulsion was found to be attended by a decrease of dimethoxydichlorovinyl phosphate, metaphos, and butyphos toxicity in rats [3]. No information is available indicating that perfluorocarbons affect the state of detoxication systems and animal resistance to GABA-lytics. The present investigation was designed to address these questions.

MATERIALS AND METHODS

The experiments were carried out on albino mice and male rats weighing 20-22 and 170-200 g, respectively. A phospholipid emulsion of perfluorodecalin (PFD) was injected intraperitoneally in a dose of 1930 mg/kg per 10 g body weight in 0.1 ml to mice and in 1 ml per 100 g body weight to rats. For mouse experiments picrotoxin (Serva) was suspended with Tween-80 in saline. The toxin was dissolved in 25% dimethylsulfoxide in rat tests. The toxicity was determined vis-a-vis the 2 h survival rate of animals after intraperitoneal injection of picrotoxin. No less than 5 doses of toxin were used and no fewer than 6 animals per dose. Diazepam (Sigma) was administered at 5 mg/kg 10 minutes prior to picrotoxin. The toxicity of picrotoxin, bicuculline, and 3-mercaptopropionic acid (Sigma) was estimated in individual series against the background of preinjected cobalt chloride (15 mg/kg i.p. 2 h before GABA-lytics). The values of LD_{50} were calculated by regression analysis with the method of least squares. The activity of detoxication systems was determined after preliminary (7 days before) PFD administration in rats. The state of the monooxygenase system was assessed from the duration of hexenal-induced sleep and the cytochrome P-450 content in the liver [1,11]. The activity of carboxylesterases, glutathione-S-transferase, uridinediphosphate-glucuronosyl transferase, superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, as well as the content of reduced glutathione and antiradical capacity of water- and fat-soluble antioxidants were determined as described elsewhere [1,4-7,9-11,13,14,16].

RESULTS

Preadministration of PFD was followed by a rise of the resistance of rodents to the toxic action of

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TABLE 1. Effect of Preliminary PFD Administration on Picrotoxin Toxicity in Rodents

Animals	Diazepam, 5 mg/kg 10 min prior to picrotoxin	Time from PFD administration, days	LD_{50}, mg/kg
Mice (control)	–	–	6.24±0.72
Mice	+	–	11.54±1.01**
"	–	7	10.30±0.84**
"	–	14	9.05±0.71*
"	–	21	7.18±0.63
"	+	7	25.58±2.84**
Rats (control)	–	–	5.63±0.71
Rats	–	7	10.11±0.91**

Note. Here and in Table 3: * $p<0.01$, ** $p<0.001$ in comparison with the control.

picrotoxin (Table 1). A reliable preventive effect was detected in mice during 14 days from the time of PFD injection. The coefficient of protection (i.e., the ratio of LD_{50} for the test and control groups) was 1.6 and 1.45 1 and 2 weeks later, respectively. A 1.8-fold increase of the resistance to the toxin was also noted in rats towards the end of the 7th day subsequent to fluorocarbon administration.

Under conditions of preliminary (7 days before) injection of inductor a boost of the antidotal activity of diazepam was noted in mice poisoned with picrotoxin. Reliable changes of GABA-lytic toxicity were absent in mice treated with cobalt chloride (Table 2).

The activity of some components of detoxication systems 7 days after PFD injection is listed in Table 3. The duration of hexenal sleep was 7.5-fold shorter in mice treated with PFD 7 days prior to the test in comparison with the control. As is evident from Table 3, under these conditions an increase was noted for a number of indexes reflecting the functional state of various detoxication mechanisms, such as hydroxylation, conjugation, and antiradical defense. The activity of monooxygenases, carboxylesterases, glutathione-S-transferase, uridinediphosphate-glucuronosyl transferase, and glutathione reductase, as well as the content of the water-soluble inhibitors of free radicals rose to the greatest extent.

Previously an increase of resistance to the toxic action of organophosphorus compounds [8] and GABA-lytics [2] was noted for rodents for preliminary barbiturate administration. Under the same conditions the activity of antidotes was also enhanced [2]. A protective effect of perfluorocarbons was demonstrated against the background of poisoning with organophosphorus compounds [3]. Our data attest to similar effects induced by GABA-lytic picrotoxin. It may be assumed that the decreased toxicity under such conditions is related to the enhanced functional capacity of xenobiotic-neutralizing systems. Probably, processes of nonspecific sorption involving blood proteins, namely serum albumin and carboxylesterases, rather than oxidation of the toxin by monooxygenases of the endoplasmic reticulum play a key role here, because the inhibitor of the above-mentioned enzymes, cobalt chloride, did not affect picrotoxin toxicity.

Attention is drawn to the fact that the effect of induction impinges upon all mechanisms of detoxication of xenobiotics - binding and transport by blood proteins, hydroxylation, conjugation, and antiradical defense. This reflects their close morphofunctional relationship [12].

Preliminary PFD administration was accompanied by an enhanced antidotal activity of diazepam for picrotoxin intoxication in mice. This is in accordance with data reported previously on an increased anticonvulsive efficacy of diazepam under conditions of phenobarbital induction [2]. This finding may be related to alteration of the functional state of the GABA-benzodiazepine-ionophore complex. The highly lipophilic PFD most probably affects the receptor indirectly via modulation of the surrounding lipid matrix.

Thus, PFD, an inductor of the phenobarbital type, enhanced resistance to the toxic action of the GABA-lytic picrotoxin in rats and mice. The an-

TABLE 2. Toxicity of GABA–Lytics against the Background of Preliminary Cobalt Chloride Administration in Mice

Substances	LD_{50}, mg/kg	
	saline	$CoCl_2$, 15 mg/kg 2 h prior to GABA-lytics
3–Mercapto-propionic acid	32.11±5.12	34.84±7.11
Bicuculline	12.44±1.38	11.64±1.50
Picrotoxin	7.62±0.74	7.01±0.63

TABLE 3. Effect of Preliminary Administration of PFD on the State of Some Components of Detoxication Systems in Rats, % of Normal State

Indexes	Liver	Serum
Total protein	–	109.3±2.5*
Serum albumin	–	108.1±4.6
Carboxylesterase	184.0±8.2**	227.4±12.1**
Content of cytochrome P–450	310.1±12.5**	–
Glutathione–S–transferase	259.5±7.3**	–
Uridinediphosphate–glucuronosil transferase	265.5±9.3**	–
Superoxid dismutase	131.9±9.3*	–
Catalase	122.1±2.3**	–
Glutathione peroxidase	115.2±4.2*	–
Glutathione reductase	204.4±10.6**	–
Reducted glutathione	129.5±4.0**	–
Water–soluble antioxidants	278.7±16.3**	–
Fat–soluble antioxidants	161.2±12.7**	–

tidotal efficacy of diazepam rose under these conditions. Preliminary perfluorocarbon administration to rats was attended by the activation of the monooxygenase, conjugation, and antioxidant detoxication systems. The protective effect of PFD may be associated with the induction of detoxication systems and primarily with the increased activity of carboxylesterases and increased protein content in the blood serum.

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