J. Pharm. Pharmac., 1966, **18**, 38–40 Received July 12, 1965

Liver function and pyrexia caused by a pyrogen from *Escherichia coli*, lysergic acid diethylamide and dinitrophenol

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Rabbits with liver damaged by carbon tetrachloride do not respond with hyperthermia to a lipopolysaccharide pyrogen from *Escherichia coli* or dinitrophenol, but lysergic acid diethylamide develops its usual effect. Rabbits with obstructive liver damage react with hyperthermia to all three pyrogenic factors. The results support the concept of a peripheral action of pyrogen. It is suggested that the liver plays a rôle in the process of transforming the bacterial pyrogen into the endogenous pyrogen.

IN our previous studies it was possible to demonstrate that a lipopolysaccharide from *Escherichia coli*, when administered *in vitro* or *in vivo* increases oxygen consumption in sections of liver (Venulet & Desperak, 1957; Desperak-Naciążek & Venulet, 1960). This effect is connected with the activation of succinic acid dehydrogenase (Venulet & Desperak-Naciążek, 1960). The rôle of liver function seems to be so important that in rabbits with carbon tetrachloride liver damage the pyrogenic response disappears during the time of positive liver function tests and reappears with their return to initial values.

Because this phenomenon might help to evaluate the significance of peripheral factors in different kinds of hyperthermia we decided to study the effects of lysergic acid diethylamide (Sandoz) and 2,4-dinitrophenol in rabbits with damaged livers.

Material and methods

In all experiments only animals with reactivity to pyrogen were used. Liver damage was developed by two different methods. In the first group, freshly distilled carbon tetrachloride was injected subcutaneously in a dose of 1·5 ml/kg. In the second group the common hepatic duct was ligated to produce obstructive liver lesion (McLuen & Fouts, 1961). As we have found previously (Venulet & Desperak-Naciążek, 1963) the peak liver damage in both types of injury is reached 72 hr after injection or ligation. The tests were still positive during the first two weeks but during the third and fourth week they gradually returned to normal.

Animals, in 3 groups, received bacterial pyrogen, lysergic acid diethylamide or dinitrophenol intravenously at weekly intervals for four weeks. The rectal temperature was measured every 30 min by thermocouples during 1 hr before and 3 hr after the injection. The results were evaluated statistically by means of the analysis of variance and the *t*-test.

Results and discussion

From Table 1 it can be seen that with both pyrogen and dinitrophenol the pyrogenic reaction disappears during the onset of liver damage but

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reappears with return of its function. The results with lysergic acid diethylamide are independent of the degree of the liver lesion, the hyperthermia persisting. These differences are statistically significant and throw new light on the rôle played by the liver in pyrogen and dinitrophenol hyperthermia and its non-participation in lysergic acid diethylamide hyperthermia.

TABLE 1. THE INFLUENCE OF CARBON TETRACHLORIDE LIVER DAMAGE ON THE PYROGEN LYSERGIC ACID DIETHYLAMIDE OR DINITROPHENOL HYPERTHERMIA

Drug and dose	No. of animals	Δ t°C						Smallest difference when P=0·95
		Before damage	After damage on day					
			4	11	18	25	32	
Pyrogen, 0·02 μg/kg ..	38	+0·85	+0·85	+0·55	+0·41	+0·59	+1·0	0·2
Lysergic acid diethylamide, 5 μg/kg	20	+0·71	+0·82	+0·80	+0·86	+0·85	+0·80	0·15
Dinitrophenol, 10 mg/kg ..	20	+0·97	+1·1	+0·52	+0·51	+0·6	+0·8	0·23

These results furnish some new evidence for the generally accepted opinion about the mechanism of action of lysergic acid diethylamide and dinitrophenol. Moreover they supply further proof for the underestimated rôle of peripheral factors in the postpyrogenic fever. It seems likely that endotoxins other than of *E. coli* origin also develop fever partially through the peripheral mechanism. The fact that on the fourth day after carbon tetrachloride injection, when the lesion is most pronounced, the fever reaction still persists to disappear only a few days later is difficult to explain. In agreement with the theory that bacterial pyrogens are either transformed into endogenous pyrogen or stimulate its production, we assume the existence of an endogenous activator which is produced by the liver and which circulates in the blood for some days, even after its production has been stopped by the carbon tetrachloride. Therefore on the fourth day its level is still high enough to start the whole reaction.

TABLE 2. THE INFLUENCE OF OBSTRUCTIVE JAUNDICE ON THE PYROGEN, LYSERGIC ACID DIETHYLAMIDE OR DINITROPHENOL HYPERTHERMIA

Drug and dose	No. of animals	Δ t°C							Smallest difference when P=0·95
		Before damage	After damage on day						
			3	7	10	14	17	21	
Pyrogen 0·02 μg/kg ..	20	1·02	1·03	1·32	1·13	1·32	0·93	0·86	0·37
Lysergic acid diethylamide 5 μg/kg ..	20	0·97	0·66	0·81	0·80	1·25	0·62	1·03	0·47
Dinitrophenol, 10 mg/kg ..	20	0·95	0·67	0·53	0·60	0·88	0·48	0·93	0·55

Table 2 shows that not all kinds of liver damage lead to the same result. In spite of highly positive liver tests in rabbits with ligated hepatic ducts, the pyrogenic response to our pyrogen, lysergic acid diethylamide or

dinitrophenol remains unchanged throughout the experiment. This indicates the complex character of the observed phenomena and the specificity of involved mechanisms. The two kinds of damage are so different in their mechanism and morphology that their consequences also differ.

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