The increases in mouse striatal tryptamine produced by parenteral administration of benzene or pyridine (Table 2) suggest that the treatment produces an induction of aromatic-L-aminoacid decarboxylase. The fact that the administration of benzene or pyridine increased the concentration of striatal 5-HIAA (Table 2) rules out the possibility that the organic solvents act by inhibition of monoamine oxidase but suggest that the treatment increases 5-HT turnover.

In conclusion, some organic solvents such as benzene or pyridine can selectively affect aromatic-L-aminoacid decarboxylase *in vitro*, as well as *in vivo* after parenteral administration; the effect *in vivo*, however, may not be the same as that *in vitro*.

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Lack of effect of several barbiturates on liver blood flow

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Liver blood flow is an important determinant of the pharmacokinetics of drugs with a high hepatic intrinsic clearance such as lignocaine and propranolol [1]. For such compounds hepatic enzyme activity is not the major determinant of the rate of hepatic elimination. It is important, therefore, to have a knowledge of the effects of drugs on liver blood flow in order to anticipate interactions with drugs whose elimination is significantly dependent on liver blood flow.

Phenobarbitone treatment has been shown not only to increase hepatic microsomal enzyme activity but also to increase liver blood flow in the rat [2–5], in the monkey [6] and in man [7]. Furthermore, this increase in hepatosplanchnic blood flow has also been shown to be responsible for that part of the increase in the hepatic elimination of indocyanine green [8] and propranolol [6] not accounted for by enzyme induction.

Amylobarbitone treatment in the rat does not increase liver blood flow despite significant enzyme induction [5]. However, the effect of other barbiturates on liver blood flow has not been reported. Therefore, we have investigated the effect of several 5-alkyl and 5-allyl barbiturates on hepatosplanchnic blood flow in the rat in order to determine whether molecular structure, the degree of enzyme induction or hepatomegaly can be correlated with the effects on blood flow.

Methods

Animals and pretreatment. Male Wistar rats weighing 220–250 g (Bantin & Kingman Ltd., Hull, U.K.) were fed on standard laboratory diet (Labsure, C. Hill Ltd., Poole, Dorset, U.K.) in drop-through cages on a 12-hr light/dark cycle. In the blood flow studies two groups of experiments were performed. In one the treatment rats received the sodium salts of either barbitone (Sigma, St. Louis, MO), amylobarbitone (Lilly, Basingstoke, Hants., U.K.) or quinalbarbitone (Sigma) dissolved in saline (0.9% NaCl) and the control animals received saline. In the other the treatment rats received either butabarbitone (Sigma), mephobarbitone (Sigma), allobarbitone (Sigma) or aprobarbitone (Sigma) dissolved in an equivalent vol. of 1 M NaOH and diluted in saline. For these animals the control group received 0.1 M NaOH in saline. All treated animals were given 120 mg/kg/day of the barbiturate intraperitoneally (i.p.) in a vol. of 4 ml/kg/day in divided doses for 5 days and the control rats were given the same vol. of vehicle (2 ml/kg) i.p. twice daily for 5 days. In the sleeping time study only one, saline, control group was used. All animals were used on the 6th day after the start of treatment and were starved for 15–20 hr before use.

Determination of liver blood flow. The rats were anaesthetised with sodium pentobarbitone (60 mg/kg i.p.; Sagatal, May & Baker, Dagenham, Essex, U.K.) and a tracheal cannula inserted. The left femoral artery was cannulated and connected to a Bell & Howell type 4-422-0001 transducer to measure systemic arterial blood pressure which was recorded on a Grass 79D polygraph. The left femoral artery was also cannulated and connected to a Braun Perfusor IV pump for the withdrawal of blood. With the aid of pressure monitoring, a cannula was passed down the right common carotid artery into the left ventricle. 60,000–80,000 ^{113}Sn labelled microspheres (15 ± 3 μm; NEN), suspended in saline containing 0.01% Tween 80, were injected into the ventricle over 20 sec. During and for 70 sec after the microsphere injection blood was withdrawn from the left femoral artery at a rate of 0.5 ml/min. Cardiac output and liver blood flow were determined as described by Nies *et al.* [4].

Pentobarbitone sleeping time. The animals were given sodium pentobarbitone (40 mg/kg, i.p.) and the time

Table 1. The effect of barbiturate treatment (120 mg/kg/day) for 5 days on liver wt and liver blood flow[1]

(a)	Saline (N = 8)	Barbitone (N = 8)	Amylo (N = 8)	Quinal (N = 8)
Liver wt (g/100 g body wt)	3.38 ± 0.10	4.11 ± 0.12**	3.57 ± 0.04	3.50 ± 0.06
Cardiac output (ml/min/100 g body wt)	20.8 ± 1.0	22.7 ± 1.9	21.5 ± 1.2	24.4 ± 1.0
% Cardiac output received by the hepatosplanchnic circulation	29.1 ± 1.7	28.2 ± 0.9	31.1 ± 2.2	31.9 ± 1.6
Liver blood flow (ml/min/100 g body wt)	6.00 ± 0.40	6.34 ± 0.40	6.69 ± 0.6	7.77 ± 0.45
(ml/min/g liver)	1.80 ± 0.14	1.54 ± 0.08	1.87 ± 0.16	2.22 ± 0.11*

(b)	NaOH (N = 8)	Buta (N = 9)	Mepho (N = 9)	Allo (N = 9)	Apro (N = 7)
Liver wt (g/100 g body wt)	3.73 ± 0.12	4.05 ± 0.09*	4.82 ± 0.11***	3.82 ± 0.04	3.68 ± 0.06
Cardiac output (ml/min/100 g body wt)	22.9 ± 1.5	24.5 ± 2.5	24.2 ± 1.3	20.5 ± 1.1	24.4 ± 2.0
% Cardiac output received by the hepatosplanchnic circulation	31.0 ± 2.0	30.6 ± 2.6	30.2 ± 1.4	30.6 ± 1.1	33.9 ± 2.2
Liver blood flow (ml/min/100 g body wt)	7.02 ± 0.45	7.07 ± 0.32	7.28 ± 0.52	6.23 ± 0.32	8.01 ± 0.37
(ml/min/g liver)	1.89 ± 0.12	1.75 ± 0.09	1.50 ± 0.09**	1.64 ± 0.09	2.17 ± 0.08

[1] Values are shown as the mean ± S.E.M. Significantly different from control: *$P < 0.05$, **$P < 001$, *** $P < 0.001$ (Analysis of variance followed by least significant difference.)

between the loss and the regaining of the righting reflex was measured.

Data analysis. All results are given as the mean ± S.E.M. and the statistical significance of differences between control and barbiturate groups was tested by analysis of variance followed by the least significant difference procedure [9].

Results

Liver blood flow. There were no significant differences between the saline and the saline/NaOH control groups with respect to liver wt, cardiac output or liver blood flow. Table 1 shows the effects of barbitone, amylobarbitone, quinalbarbitone, butabarbitone, mephobarbitone, allobarbitone and aprobarbitone on liver blood flow. None of the barbiturates had any significant effect on cardiac output or the proportion of the cardiac output received by the hepatosplanchnic circulation. As a result there were no significant changes in absolute liver blood flow or in flow relative to body wt. However, liver wt was significantly increased by barbitone (21%), butabarbitone (9%) and mephobarbitone (29%). Although blood flow relative to liver mass tended to fall with these compounds this was only significant for mephobarbitone.

Sleeping time. Pentobarbitone sleeping time was significantly shorter in the barbitone (12.8 ± 4.2 min, $P < 0.001$), butabarbitone (10.5 ± 10.5 min, $P < 0.01$), aprobarbitone (25.6 ± 12.8 min, $P < 0.01$), mephobarbitone (26.6 ± 4.8 min, $P < 0.01$) and allobarbitone (37.0 ± 1.9 min, $P < 0.05$) treated animals than in the control group (60.4 ± 5.8 min) but was not significantly different in the quinalbarbitone (50.0 ± 3.8 min) or amylobarbitone (63.4 ± 4.3 min) groups (N = 4 for all groups).

Discussion

This study was undertaken in order to determine, if possible, some structure/activity relations for barbiturates on liver blood flow. However, none of the seven, structurally diverse, barbiturates studied here had any significant effects on cardiac output or its relative distribution and hence did not affect liver blood flow relative to body wt. The reason for this lack of effect is unclear. All the barbiturates used, with the exception of barbitone, produced hypnosis thus showing that effective doses had been used. Further, butabarbitone, barbitone and mephobarbitone significantly increased liver size, to the extent that perfusion per unit mass of liver was reduced. In view of the increase in liver wt with these three agents we are able to conclude that barbiturate induced hepatomegaly does not necessarily increase liver blood flow.

We examined the effect of the barbiturates on pentobarbitone sleeping time in order to determine whether or not the compounds under investigation were having any effect on liver function. Ioannides and Parke [10] have shown that three of the agents used in the present study, quinalbarbitone, allobarbitone and barbitone, at a dose of 75 mg/kg daily for 3 days, induce a range of liver microsomal enzymes. They also showed that there was a close agreement between the ability of a barbiturate to reduce hexobarbitone sleeping time *in vivo* and its effects on microsomal enzyme activity *in vitro* [10]. Thus, despite the indirect nature of this test, reductions in sleeping time probably closely reflect the degree of hepatic enzyme induction rather than cellular tolerance especially since plasma pentobarbitone concentration on awakening in rabbits is not affected by barbiturate pretreatment [11]. In the present study, all except two of the compounds investigated reduced sleeping time and thus, since liver blood flow was unchanged, presumably gave some degree of hepatic enzyme induction. Therefore the lack of effect of these agents on liver blood flow cannot be ascribed to a failure to increase either liver size or its drug metabolising function.

The barbiturates used in this study are structurally diverse but one is particularly similar to phenobarbitone which has previously been shown to increase liver blood flow by several groups of workers, including our own [3–5]. Mephobarbitone is *N*-methyl phenobarbitone but we did not find that it affected liver blood flow despite causing marked hepatomegaly and greatly reducing pentobarbitone sleeping time. Therefore, there do not appear to be any simple structural changes that may be made in order to bring about gradual changes in the effects of barbiturates on liver blood flow.

In conclusion, increasing liver blood flow is not a property possessed by the barbiturates as a class of compounds. Further, just as the induction of hepatomegaly and liver microsomal enzymes are unrelated for these compounds [12], neither of these actions of the barbiturates are associated with changes in liver blood flow.

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