ites penetrate the blood brain barrier (Baraldi 1979; Maggi & Enna 1979). However, THIP is not a substrate for GABA transaminase in vitro (Krogsgaard-Larsen et al 1979). As our study demonstrates, after an initial redistribution THIP disappears very slowly from plasma and few metabolites accumulate in the brain (Table 2). The difference in the pharmacokinetics of THIP and muscimol may very well account for the highest efficiency and lowest toxicity of THIP when this drug is administered systemically.

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The route of administration of imipramine as a factor affecting formation of its metabolite desipramine

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The results of Nagy (1977) and Van Wijk (1977) suggested that the route of administration of the tricyclic antidepressant drug imipramine can significantly modify its metabolism, distribution and pharmacokinetic parameters. After its oral administration the level of its metabolite, desipramine, in rat brain was much higher than that after intramuscular administration of the same dose of drug. To supplement their data, we have made a more detailed study, to find how the route of administration of imipramine and dosage schedule can affect the drug's metabolism and pharmacokinetics. Imipramine's distribution in the rat is similar to that in man, there being a high affinity for brain tissue and low affinity for blood. We have measured the concentration of imipramine and desipramine in blood plasma and brain tissue simultaneously to see if there is a relationship between the plasma and cerebral concentration of the two drugs.

Materials and methods

Male Wistar rats, 180–200 g, used in chronic experiments received standard granulated diet, those in acute experiments were deprived of food for 18 h before use, but had free access to water. Five to seven animals were used for each analytical point.

Imipramine hydrochloride (Tarchomin, Polfa) was given at a dose of 20 mg kg^{-1} intraperitoneally or orally as an aqueous solution. Chronic treatment consisted of daily administration of the dose at the same time of the day, for 14 days.

The animals were decapitated at predetermined times after imipramine, the trunk blood was collected in heparinized tubes and the brains were dissected and stored in solid CO_2 until assayed within 24 h.

The blood and brain levels of imipramine and desipramine were assayed according to Dingell et al (1964). The sensitivity of the method was 0·05 μg/sample for imipramine and 0·07 μg/sample for desipramine, recovery for both compounds was approx. 76%.

Pharmacokinetic parameters $t_{0.5}$, AUC were calculated using a Nonlin-Autoan 2 program (Sedman & Wagner 1976).

The results were evaluated statistically using Student's *t*-test.

Results and discussion

After single i.p. treatment with imipramine the drug reached maximal brain concentration in 35 min, it also disappeared rapidly and after 24 h there was no detectable amount in the c.n.s. The course of accumulation and disappearance of desipramine differed from those of imipramine. The C_{max} appeared 1 h after injection of imipramine, after 24 h there being ca 0·4 μg g^{-1} of desipramine in brain tissue (Fig. 1, Table 1).

* Correspondence

The brain levels of both drug and metabolite after oral administration were significantly lower than those observed after intraperitoneal administration. After the single oral dose, imipramine reached the brain more slowly than after the i.p. dose and its half life was increased. Desipramine appeared in the brain rapidly, reaching maximal concentration after 3 h, its half life was also longer, after 24 h there being the same level of desipramine as that observed after i.p. administration (Fig. 1, Table 1).

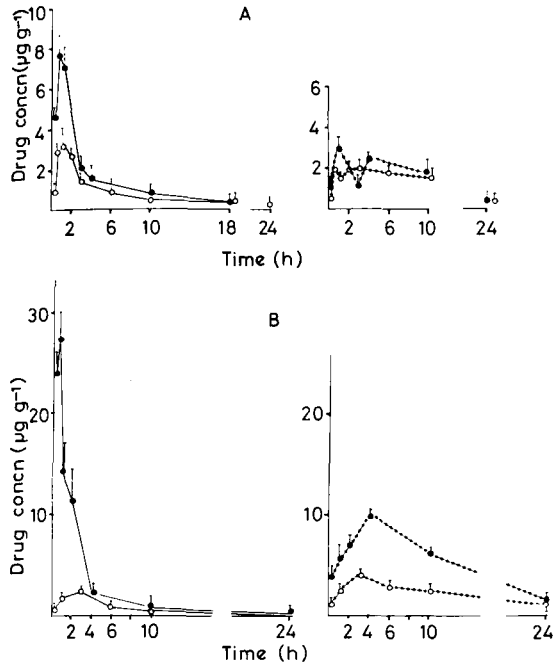

FIG. 1. Time course of imipramine and desipramine brain levels after A—single, B—chronic intraperitoneal and oral administration of 20 mg kg^{-1} of imipramine. Imipramine i.p. ●——●, oral ○——○; desipramine after imipramine i.p. ● . . ● and oral ○ . . ○. Each point represents the mean ± s.e.m. of 5–7 animals.

Chronic intraperitoneal treatment with 20 mg kg^{-1} of imipramine did not change its t_{max} but markedly affected brain C_{max} value which increased four times compared with the single dose. As in the acute experiment, imipramine disappeared rapidly from the brain and it was not detectable after 24 h. Brain accumulation of desipramine differed from that after the single dose of imipramine. The C_{max} of the metabolite appeared after 4 h and its value was much higher but the rate of its disappearance was nearly the same as that after the single i.p. dose of imipramine (Fig. 1, Table 1).

After chronic oral treatment the levels of drug and metabolite in brain were significantly lower than the corresponding i.p. values, but compared with the results after the single oral dose, the level of imipramine decreased while the level of desipramine increased, the C_{max} of both compounds being 3 h after the last dose of imipramine. Their rate of disappearance was slowed to such extent that after 24 h there was ca 1 μg g^{-1} of metabolite and 0·3 μg g^{-1} of parent compound (Fig. 1, Table 1).

The plasma levels of both drug and metabolite, independently of the route of administration and dosage schedule, were significantly lower than corresponding levels in the brain. Their plasma pharmacokinetics also differed from those in brain. Chronic treatment increased the levels of both parent compound and metabolite and markedly prolonged their half lives. The plasma levels of both compounds after chronic oral treatment did not change with the time and, in contrast to the brain the level of imipramine, exceeded or equalled that of desipramine (Fig. 2, Table 1).

Table 1. C_{max}, t_{max} and $t_{0.5}$ values of imipramine and desipramine in the rat brain and plasma after single and multiple administration of imipramine in a dose of 20 mg kg^{-1} i.p. or orally.

Tissue and route	Imipramine						Desipramine					
	Single dose			Multiple dose			Single dose of imipramine			Multiple dose of imipramine		
	C_{max} μg g^{-1} ml^{-1}	t_{max} h	$t_{0.5}$ h	C_{max} μg g^{-1} ml^{-1}	t_{max} h	$t_{0.5}$ h	C_{max} μg g^{-1} ml^{-1}	t_{max} h	$t_{0.5}$ h	C_{max} μg g^{-1} ml^{-1}	t_{max} h	$t_{0.5}$ h
Brain i.p.	7·8 ± 1·0	0·5	1·6	27·3 ± 1·5[a]	0·5	1·9	3·2 ± 0·5	1·0	4·6	10·1 ± 0·3[a]	4·0	4·8
Brain oral	3·2 ± 1·1	1·0	3·8	2·3 ± 0·5[b]	3·0	4·0	2·0 ± 0·3	3·0	11·9	4·2 ± 0·3[a]	3·0	12·7
Plasma i.p.	1·0 ± 0·3	0·5	0·8	3·5 ± 1·6[a]	0·5	21·6	1·0 ± 0·1	1·0	2·8	1·7 ± 0·8	0·5	17·7
Plasma oral	0·6 ± 0·2	1·0	3·8	0·5 ± 0·2	1·0	10·8	0·9 ± 0·1	4·0	2·9	0·4 ± 0·3	1·0	77·0

[a] $P < 0·001$ compared with corresponding C_{max} after single dose of imipramine.
[b] $P < 0·05$ compared with C_{max} of imipramine after single dose of imipramine.

The rate of disappearance of both compounds from the brain and plasma, their C_{max} values, and area under the curve (AUC) values in brain and the ratio AUC_{DMI}:

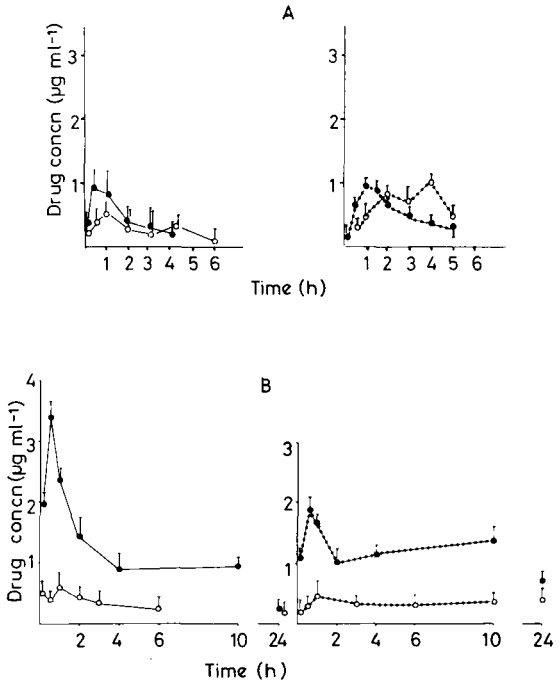

FIG. 2. Time course of imipramine and desipramine plasma levels after A—single, B—chronic intraperitoneal and oral administration of 20 mg kg^{-1} of imipramine. For key see Fig. 1.

Table 2. AUC values of imipramine (IMI) and desipramine (DMI) in rat plasma and brain after single and prolonged administration of imipramine intraperitoneally and orally in a dose of 20 mg kg^{-1}.

Tissue and dosage schedule	AUC_{IMI}	AUC_{DMI} ($\mu g\ h^{-1}\ g^{-1}$ or $\mu g\ h^{-1}\ ml^{-1}$)	AUC_{DMI}/AUC_{IMI}
Brain			
1 × 20 mg kg^{-1} i.p.	65·55	89·20	1·36
1 × 20 mg kg^{-1} oral	37·82	57·05	1·50
14 × 20 mg kg^{-1} i.p.	138·50	287·00	2·07
14 × 20 mg kg^{-1} oral	39·20	112·50	2·85
Plasma			
1 × 20 mg kg^{-1} i.p.	2·49	3·99	1·59
1 × 20 mg kg^{-1} oral	3·61	6·37	1·76
14 × 20 mg kg^{-1} i.p.	23·33	44·03	1·88
14 × 20 mg kg^{-1} oral	8·97	37·77	4·20

AUC_{IMI} depended on the route of administration and dosage schedule (Table 1, 2). Chronic treatment by both routes prolonged the half lives of both compounds in plasma and slightly in brain, and also increased their C_{max} values. AUC_{DMI} values after intraperitoneal injection were twice as high as those after oral administration while chronic treatment by either route increased AUC_{DMI} values in brain and plasma.

Our results indicate that the route of administration and dosage schedule affect the pharmacokinetics and biotransformation of imipramine. After chronic intraperitoneal or oral treatment the levels of both drug and metabolite were significantly higher than the corresponding levels after a single dose of imipramine, and 24 h after the last dose given chronically the brain and plasma levels of desipramine and plasma level of imipramine were high enough to inhibit the uptake of noradrenaline in brain slices (acc. to Ross & Reneyi 1975, IC50 values for imipramine and desipramine were 0·039 and 0·018 μg g^{-1} respectively). The ratios of imipramine : desipramine concentrations in plasma and brain were different, their plasma levels were significantly lower than the corresponding levels in brain and their plasma half lives differed markedly from those for brain. This suggests that changes in blood concentrations of the drugs with time do not reflect their concentrations in c.n.s.

The brain and plasma levels of imipramine and desipramine and their AUC values were much lower after oral than after intraperitoneal administration, their elimination was decreased and their levels, particularly in the plasma, did not change markedly with time within 24 h. This is probably a first pass phenomenon. According to previous literature data (Gram & Christiansen 1975; Dencker et al 1976; Bickel & Weder 1968) imipramine demethylation occurs on the first passage through the liver in both man and rat.

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