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A Comparative Study on Desipramine Pharmacokinetics in the Rat Brain after Administration of Desipramine or Imipramine

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Abstract—Chronic intraperitoneal administration of desipramine led to an extensive cumulation of the drug in brain and blood compared with that after a single dose treatment, while chronic treatment with desipramine by the oral route produced a brain concentration comparable with its level after a single oral dose. Comparison of the present results with the corresponding data of published imipramine pharmacokinetics indicated that the cumulation of desipramine in the rat brain was nearly the same when rats received desipramine or imipramine twice a day for two weeks at a dose of 10 mg kg^{-1} orally, or imipramine, twice a day for two weeks at a dose of 10 mg kg^{-1} intraperitoneally. It is suggested that these three experimental paradigms may be used as models for differentiation of the pharmacological effects of imipramine and desipramine in-vivo.

Imipramine and desipramine are frequently used in psychopharmacological experiments as model substances with well-defined pharmacological and biochemical effects in experimental animals (for review see Maj et al 1984).

The pharmacokinetics of imipramine and desipramine after different routes of administration and a diverse dosage schedule have been studied extensively in man and animals (Hammer & Sjoqvist 1967; Bickel & Minder 1970; Jori et al 1971; Hrdina & Dubas 1981; Daniel et al 1982). The biotransformation of imipramine to desipramine in rats depends on the route of administration and the dosage schedule of imipramine (Daniel et al 1982; Maj et al 1982). Consequently, the ratios between the total amount of imipramine and the total amount of desipramine, expressed as the corresponding area under the curve (AUC) values in the rat brain, differed significantly when comparing intraperitoneal (i.p.) with oral (p.o.) administration or acute with chronic treatment (Daniel et al 1982). This finding is considered to be important, as in pharmacological experiments imipramine and desipramine are usually administered i.p. to animals, while in the clinic those drugs are not administered by this route. Hence the i.p. injection of imipramine is not an adequate model for the clinical situation, at least from the pharmacokinetic point of view. As desipramine contributes to the therapeutic effect of imipramine and these agents have a different mechanism of action on the neuronal uptake (Ross & Renyi 1975) the interpretation of the results may be unreliable.

As a comparative study on desipramine pharmacokinetics in the rat after administration of imipramine or desipramine by different routes and according to various dosage schedules has not yet been conducted, it seems of interest to study the distribution of desipramine in the brain and blood plasma of rats after administration of different single and multiple doses of the drug and to compare the results with the previously published data (Daniel et al 1981; Maj et al 1982) on the pharmacokinetics of imipramine and desipramine in rats after single and multiple doses of imipramine given i.p. or p.o. Such a study might help to find a proper dose, route and dosage schedule for imipramine and desipramine leading to a similar cumulation of desipramine in the rat brain which, in turn, might exclude involvement of pharmacokinetic variations when the results obtained in various experimental models are compared.

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Materials and Methods

Animals

Male Wistar rats, 200±20 g, were fed on a standard granulated diet (Bacutil), with free access to tap water.

Experimental

Desipramine hydrochloride (Serva, Heidelberg) was given to rats according to the following dosage schedules: (a) single dose of 10 or 20 mg kg^{-1} i.p. or p.o.; (b) for two weeks in a daily dose of 10 or 20 mg kg^{-1} i.p. or p.o.; (c) for two weeks twice a day in a dose of 10 mg kg^{-1} p.o.

The rats were killed by decapitation at different time intervals after administration of desipramine. Blood was collected into heparinized tubes and the brain was dissected and stored in solid carbon dioxide until desipramine assessment.

Desipramine was assayed spectrofluorometrically (Dingell et al 1964). The area under the curve from 0 to 24 h (AUC) was calculated graphically with the trapezoidal rule from response curves plotted on a linear time scale. The highest mean concentration of desipramine obtained was defined as C_{max}.

Results

When given to rats in a single dose of 10 mg kg^{-1} i.p., desipramine rapidly penetrated the rat brain, reaching the maximum concentration (approx. 3·3 μg (g of the wet tissue)$^{-1}$) 30 min after administration, i.e. at the same time as

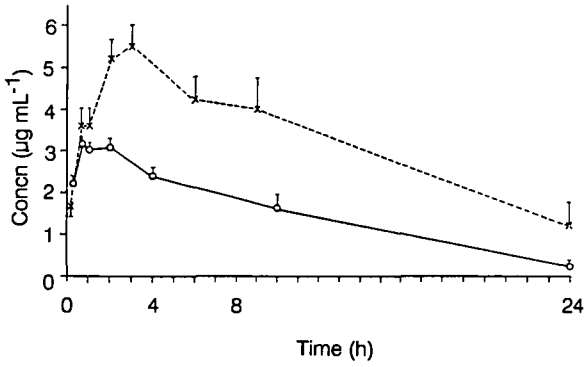

FIG. 1. Time-concentration curve of desipramine in the rat brain after i.p. administration of desipramine in a single, 1 × 10 mg kg^{-1} (○), or multiple, 14 × 10 mg kg^{-1} (×) dose. The results are presented as the mean + s.e.m. of 6 rats.

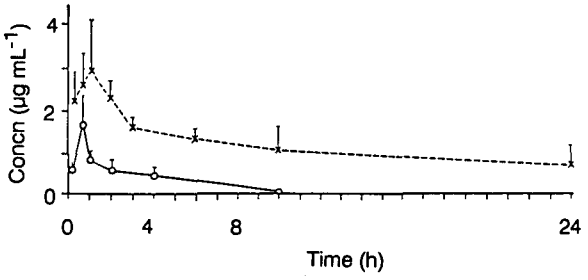

FIG. 2. Time-concentration curve of desipramine in the blood plasma of rats after i.p. administration of desipramine in a single, 1 × 10 mg kg^{-1} (○), or multiple, 14 × 10 mg kg^{-1} (×) dose. The results are presented as the mean + s.e.m. of 6 rats.

in the blood plasma, yet its value was approximately twice that in the blood. Chronic treatment of rats with desipramine at the same dose of 10 mg kg^{-1} i.p. led to an extensive cumulation of the drug in the brain—the corresponding C_{max} and AUC values after prolonged administration of desipramine having increased by ca. 100%, when compared with those after administration of the agent as a single dose of 10 mg kg^{-1} i.p. (Fig. 1). The same extensive cumulation of desipramine after chronic administration of the agent was found in the blood plasma of rats and, as for the single-dose treatment, the ratio between the brain and blood plasma levels of the drug in chronically treated animals was approximately 2 (Fig. 2).

In contrast to i.p. administration, chronic p.o. administration of desipramine at a dose of 20 mg kg^{-1} did not result in cumulation of the drug in the rat brain, when compared with single-dose treatment. The corresponding brain C_{max} and AUC values after acute and chronic treatment with desipramine in a dose of 20 mg kg^{-1} by the oral route were very similar (4·75 and 5·50 μg g^{-1}, and 78·65 and 85·80 μg h g^{-1}, respectively) (Fig. 3).

When desipramine was given to rats p.o. twice a day at a dose of 10 mg kg^{-1}, C_{max} (4·00 μg g^{-1}) in the brain was similar to that after p.o. administration of the drug, 2 h after the last dose of desipramine. The time-concentration curve of the drug after this dosage schedule resembled the time-concentration curve of desipramine after single rather than that after prolonged administration of the drug at a dose of 20 mg kg^{-1} p.o. (Fig. 4a).

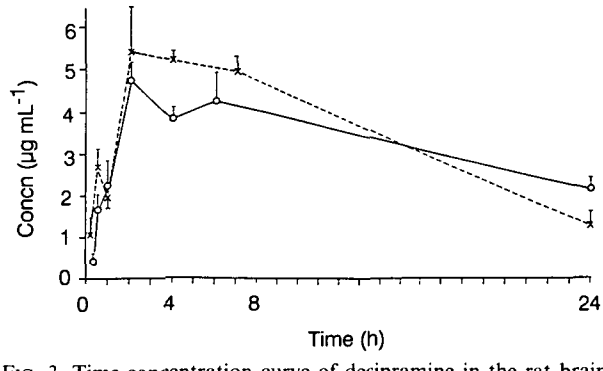

FIG. 3. Time-concentration curve of desipramine in the rat brain after oral administration of desipramine in a single, 1 × 20 mg kg^{-1} (○), or multiple, 14 × 20 mg kg^{-1} (×) dose. The results are presented as a mean + s.e.m. of 6 rats.

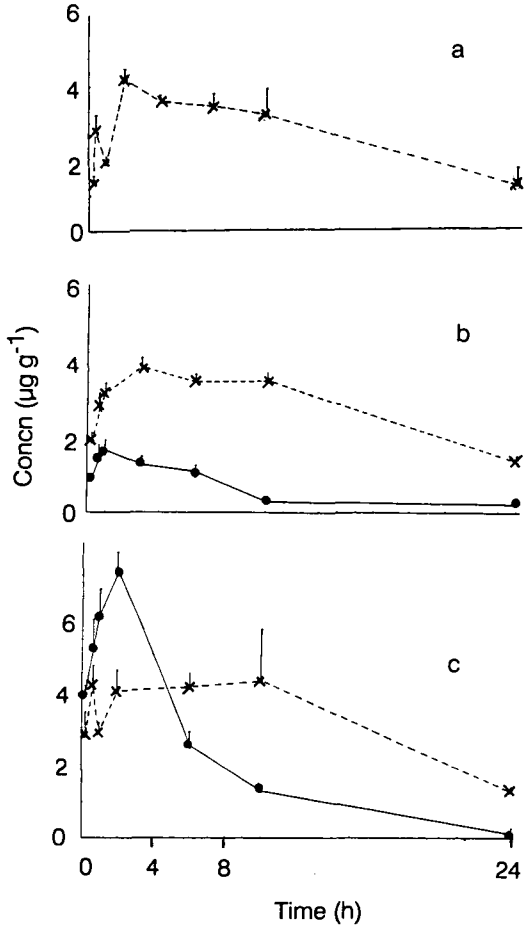

FIG. 4. Time-concentration curves of desipramine and imipramine in the rat brain after administration of: a, desipramine twice a day for two weeks at a dose of 10 mg kg^{-1} p.o. (×). The results are presented as the mean + s.e.m. of 6 rats. b, Imipramine twice a day for two weeks at a dose of 10 mg kg^{-1} p.o. (●, imipramine; ×, desipramine) (according to Maj et al (1982)). c, Imipramine twice a day for two weeks at a dose of 10 mg kg^{-1} i.p. (●, imipramine; ×, desipramine) (according to Daniel et al (1981)).

Discussion

Imipramine and desipramine are frequently used as model substances in psychopharmacological experiments; however, the mode and site of their action in the central nervous

system (CNS) is still unclear. Desipramine is an inhibitor of neuronal noradrenaline uptake, while imipramine inhibits both noradrenaline and 5-hydroxytryptamine (5-HT) uptake (Ross & Renyi 1975). In the early 1980s the presence of [^{3}H]imipramine and [^{3}H]desipramine binding sites was established in the brain and peripheral tissues, which were assumed to be relevant modulatory sites for 5-HT ([^{3}H]imipramine sites) or noradrenaline ([^{3}H]desipramine sites) uptake (Langer et al 1981; Brunello et al 1982). Therefore the ratio between imipramine and desipramine in the brain may be of pharmacological or even therapeutic importance.

Apart from the mechanism of action of imipramine or desipramine, it is clear that their therapeutic effect is associated with chronic effects, i.e. that a long-lasting exposure of the target (CNS) to either drug is necessary to achieve improvement in patients. Therefore, if the situation in the clinic is to be simulated, pharmacological experiments with imipramine or desipramine should be carried out after chronic, rather than acute, treatment with the drugs. For this reason we were particulary interested in the desipramine pharmacokinetics in the rat brain after chronic administration of desipramine or imipramine.

Our study showed that after administration of desipramine, irrespective of the dosage schedule of the agent, the drug reached the rat brain rapidly and it cumulated in the brain to a considerably greater extent than in the blood plasma. This finding is in agreement with some earlier results of other authors (Jori et al 1971; Van Wijk et al 1977; Hrdina & Dubas 1981; Daniel et al 1982).

We also found that cumulation of desipramine in the rat brain after chronic i.p. administration of the drug was higher than after acute i.p. treatment. This phenomenon may be explained by inhibition of desipramine metabolism after chronic treatment with the drug. It was previously found (Daniel & Melzacka 1987; Daniel & Netter 1990) that prolonged administration of imipramine to rats decreased the imipramine and desipramine hydroxylase activity in liver microsomes; however, on the basis of our pharmacokinetic results, overlapping of the subsequent doses of desipramine also seems to occur. In addition, the increased desipramine cumulation in the rat brain after chronic administration of the drug may be due to the phospholipidosis induced by prolonged exposure of the tissues to desipramine which leads to an increased cumulation of amphiphilic drugs in the brain and other tissues (Lüllmann-Rauch 1979; Honegger et al 1983).

This considerably higher cumulation of the drug in the rat brain after prolonged adminstration did not occur when chronic desipramine was given to rats orally. The corresponding C_{max} and AUC values of desipramine in the rat brain after acute and chronic p.o. treatment with a dose of 20 mg kg^{-1} were similar. This finding may suggest a decrease in the desipramine bioavailability when the drug is given to rats chronically by the oral route. A comparison between the pharmacokinetic data from the blood plasma after imipramine administration to rats according to different dosage schedules (Daniel et al 1982) seems to support this hypothesis. When imipramine was given to rats i.p., the total amount of the parent compound (imipramine) and its metabolite (desipramine) in the blood plasma after a two-week treatment with imipramine increased more than three times, when compared with administration of the single dose (20 mg kg^{-1}, i.p.). On the other hand, when imipramine was given to rats at a dose of 20 mg kg^{-1} p.o., the total amount of imipramine and desipramine in the blood plasma after a two-week treatment was almost the same as after the single oral dose. The decreased bioavailability of desipramine after chronic oral administration of the drug might be due to the diminished permeability of the gut wall for desipramine. Chronic exposure of different tissues to cationic amphiphilic drugs, such as desipramine, produces lipidosis (Lüllmann-Rauch 1979) which, in turn, may induce profound changes in the permeability of the membranes for amphiphiles (Lüllmann-Rauch 1979). However, it cannot be excluded that the phenomenon originates in an increased metabolism of desipramine in the gastrointestinal tract, gut wall or gastrointestinal lumen during chronic oral administration of the drug, which may mask the inhibitory effect of imipramine and desipramine on the hydroxylation processes in the liver (Daniel & Melzacka 1987; Daniel & Netter 1990). According to Minder et al (1971), imipramine may undergo *N*-demethylation to a relatively high degree in the gastrointestinal lumen before reaching the general circulation; however, no data are available on the desipramine hydroxylation in the gastrointestinal tract.

The time-concentration curves of desipramine in the rat brain after a single, oral dose of 20 mg kg^{-1} and after chronic treatment with a dose of 10 mg kg^{-1} p.o. twice a day were similar. Therefore, these two experimental paradigms might be used as a good model for the differentiation of the pharmacological effects of acute and chronic desipramine in rats, as the only parameter which differs between the paradigms is the time of tissue exposure to desipramine.

A comparison of the results obtained after administration of desipramine p.o. twice a day for two weeks with those after chronic administration of imipramine according to the same dosage schedule as that of desipramine (Maj et al 1982) and after chronic adminstration of imipramine twice a day at a dose of 10 mg kg^{-1} by the i.p. route (Daniel et al 1981) indicates that cumulation of desipramine in the rat brain in the three experimental paradigms is virtually the same (Fig. 4). However, the brain level of imipramine differed significantly when the drug was given to rats chronically, twice a day, by i.p. or p.o. routes, being much higher when imipramine was given i.p. The three experimental paradigms show three extreme pharmacokinetic situations in the rat brain (see Fig. 4): (a) the lack of imipramine and a moderate level of desipramine (two-week treatment with desipramine twice a day p.o.); (b) a relatively low level of imipramine and a moderate level of desipramine (when imipramine was given chronically twice a day p.o.); (c) a relatively high level of imipramine and a moderate level of desipramine (when imipramine was given for two weeks twice a day i.p.). Assuming that the effects of imipramine and desipramine on the central monoaminergic systems are different these three experimental paradigms may be used as models for differentiation of the pharmacological effects of imipramine and desipramine in-vivo.

It was found earlier that proadifen inhibited imipramine *N*-demethylation in rats (Maj et al 1981). Therefore when proadifen is used jointly with imipramine, the ratio between imipramine and desipramine in the rat brain can be regu-

lated. However, proadifen has an extremly broad spectrum of enzymatic inhibition, hence administration of this non-specific inhibitor, especially chronically, results in profound biochemical changes in the organism, which, in turn, could alter pharmacological effects of the drugs.

The present results show the importance of pharmacokinetic studies for pharmacological research, in particular when the investigated drug is biotransformed to a metabolite with a different pharmacological profile.

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