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Regional Distribution of Imipramine, Desipramine and Specific [^{3}H]Desipramine Binding Sites in the Rat Brain after Acute and Chronic Treatment with Imipramine

WLADYSLAWA DANIEL, LEOKADIA DANEK, LUCYNA JANCZAR, HALINA NOCON AND MIROSLAWA MELZACKA

Department of Pharmacokinetics and Drug Metabolism, Institute of Pharmacology, Polish Academy of Sciences, 31-343 Krakow, Poland

Abstract—Regional distribution of imipramine, desipramine and specific [^{3}H]desipramine binding sites in the rat brain after acute and chronic treatment of rats with imipramine has been investigated. Both substances were distributed unevenly within rat brain after single and prolonged administration of imipramine. This was partly connected with the regional cerebral blood flow, lipid content in the regions and lipophilicity of the substances investigated. It was also found that the number of specific [^{3}H]desipramine binding sites was different in the various brain areas, and that prolonged administration of imipramine led to a decrease of their number in some of those regions. No correlation was found between the regional cerebral distribution of desipramine and the regional density of specific [^{3}H]desipramine binding sites.

The tricyclic antidepressant drug imipramine is subjected to multiple biotransformation in the rat yielding, among other metabolites, desipramine (Bickel & Weder 1968). The lipophilic character of both molecules promotes their accumulation in lipid-rich organs, e.g. in the brain (Potter et al 1979; Daniel et al 1981, 1982; van Wijk & Korf 1982).

Little is known about the regional distribution of imipramine and desipramine within the central nervous system (CNS) of rats after single or prolonged administration of imipramine; however, the available data indicate that both these drugs, at least after a single dose of imipramine, are unevenly distributed within rat brain (Sherman & Allers 1980; van Wijk & Korf 1982; Barkai et al 1984).

The results of recent studies indicate the existence of specific binding sites of imipramine and desipramine associated with 5-HT-ergic neurons (imipramine) (Langer et al 1980; Barbaccia et al 1983) or noradrenergic neurons (desipramine) (Raisman et al 1982; Biegon & Rainbow 1983) in the CNS of rats and it is postulated that they regulate the uptake of 5-HT and noradrenaline (NA) (Langer & Raisman 1983). It was also found that their regional distribution within rat CNS was not uniform (Biegon & Samuel 1979; Palkovits et al 1981).

At present it is difficult to determine whether there is a link between imipramine or desipramine concentration in particular brain areas and the regional distribution of their specific binding sites. Although the amount of either drug bound specifically to the membrane preparation in-vitro is small in comparison with their in-vivo level in particular brain regions (fmol (mg protein)$^{-1}$ and nmol (mg protein)$^{-1}$, respectively), the law of mass action should not be completely invalid in this system, particularly in the steady-state, and the fraction of either drug bound specifically in a given brain area should be proportional to the tissue concentration of that drug.

Correspondence to: M. Melzacka, Department of Pharmacokinetics and Drug Metabolism, Institute of Pharmacology, Polish Academy of Sciences, 31-343 Krakow, Poland.

To investigate the possible relationship between the tissue concentration of desipramine and the number of its specific binding sites in particular regions of the rat brain we examined the regional distribution of both drugs in the rat CNS after acute and chronic treatment with imipramine concomitantly with a corresponding binding study of labelled desipramine in the brain areas in which the levels of both drugs had been assayed. The previous study of distribution and localization of [^{3}H]desipramine specific binding sites in rat CNS were carried out in Sprague Dawley rats which differ from Wistar rats in some biochemical responses (Vetulani, personal communication). As Wistar rats are commonly used in Poland it seemed necessary to have our own data concerning imipramine and desipramine distribution and the distribution of [^{3}H]desipramine specific binding sites in the brain of Wistar rats for the correct interpretation of pharmacological or biochemical results obtained in this Institute.

Materials and Methods

Drugs

Imipramine hydrochloride (Tarchomin, Polfa) and desipramine hydrochloride (Serva) were used.

Methods

Male Wistar rats, 250 ± 50 g, fed on a standard granulated diet (Bacutil), with free access to tap water, received imipramine (dissolved in redistilled water) in a single dose of 20 mg kg^{-1} i.p., or in the same dose and by the same route daily for 14 days. The rats were decapitated 30 min (fast-disposition phase) or 4 h (slow-disposition phase) after administration of the single dose, or 8 h (elimination phase under steady-state conditions corresponding pharmacokinetically to the slow-disposition phase in acutely treated animals) after administration of the last dose of the drug to chronically-treated animals. The brain was isolated and dissected into cortex, limbic forebrain, hippocampi, striatum, thalamus + hypothalamus brain stem and cerebellum.

The tissues were stored on solid CO_2 for no longer than 24 h until assayed spectrofluorometrically (Dingell et al 1964).

Binding studies were performed on a crude membrane preparation (P_2) of the cortex, hippocampi, striatum and cerebellum of rats treated with a single or multiple dose of imipramine (1 or 14×20 mg kg^{-1} i.p.), or of control animals treated with redistilled water only. The animals were killed 24 h after dosing. P_2 was prepared according to standard methods, i.e. homogenization in 10 vol of ice cold 0·32 M sucrose, followed by centrifugation at 750 *g* for 10 min and recentrifugation of the supernatant at 20000 *g* for 20 min. The resulting pellet was resuspended in Tris-KCl buffer (pH 7·4), centrifuged and stored until assessment at −25°C. The protein concentration (Lowry et al 1951) of the final sample was between 0·85 and 1·40 mg mL^{-1}. [^{3}H]Desipramine binding was determined by the methods of Biegon & Samuel (1979) and Raisman et al (1982) by incubation of aliquots of the membrane suspension in Tris-KCl buffer (pH 7·4) with different concentrations (0·1–6 nM) of [^{3}H]desipramine (70·1 Ci $mmol^{-1}$, NEN, England), for 30 min at 25°C (final volume of the sample was 1 mL). The mixture was filtered through a GF/C paper; the filters were washed 4 times with 3 mL of cold Tris-KCl buffer and were then transferred to vials, shaken with scintillation fluid and counted in a Beckman LS-3801 scintillation counter at 40% efficiency.

The specific binding was defined as the difference between the total binding of [^{3}H]desipramine and the binding in the presence of 100 μM non-radioactive drug.

The results were assessed statistically using analysis of variance followed by Dunnet's test.

Results

When given to rats in a single dose of 20 mg kg^{-1} i.p., imipramine was distributed unevenly within the investigated brain regions. At 30 min after administration (fast-disposition phase) the highest levels of drug and metabolite were found in the striatum, the lowest in the cortex. The ratio of the desipramine to imipramine level in most of the regions investigated was similar, being approximately 0·5 (Fig. 1, Table 1).

Table 1. The desipramine/imipramine ratio in different regions of the rat brain after administration of imipramine in a single (20 mg kg^{-1} i.p.) or multiple (14×20 mg kg^{-1} i.p.) dose in the fast-disposition phase (A), in the slow disposition phase (B) and in the elimination phase under steady-state conditions (C).

Region	A	B	C
Cortex	0·57	2·04	2·00
Hippocampi	0·53	1·35	2·33
Striatum	0·50	3·03	2·09
Limbic forebrain	0·64	2·38	2·17
Thalamus + hypothalamus	0·51	2·17	1·92
Cerebellum	0·63	3·29	3·91
Brain stem	0·72	2·31	3·98

At 4 h after imipramine administration (slow-disposition phase) of a single dose of 20 mg kg^{-1} the level of both drugs in the areas investigated was much lower than the respective levels at the fast-disposition phase. A relatively high level of imipramine was found in the cortex and hippocampi, while the highest content of desipramine occurred in the striatum. The ratio of desipramine to imipramine concentration in particular areas increased 4–6 times (depending on the region) in comparison with that found 30 min after imipramine administration, but it was similar (approx. 2·0) in the cortex, limbic forebrain, thalamus + hypothalamus and brain stem (Fig. 2, Table 1).

At 8 h after the last dose of imipramine (elimination phase under steady-state conditions) given to rats for 14 days (14×20 mg kg^{-1} i.p.) both drugs were still unevenly distributed in the areas investigated. In particular, a low level of the drugs was found in the cortex, while the hippocampi, striatum and limbic forebrain were characterized by a relatively high concentration of both. The ratio of the desipramine to imipramine level in particular regions was comparable with the corresponding ratios at the slow-disposition phase and amounted to ca 2·00 in the cortex, hippocampi, striatum, limbic forebrain and thalamus + hypothalamus (Fig. 3, Table 1).

The number of [^{3}H]desipramine specific binding sites in the cortex, hippocampi and cerebellum of control animals did

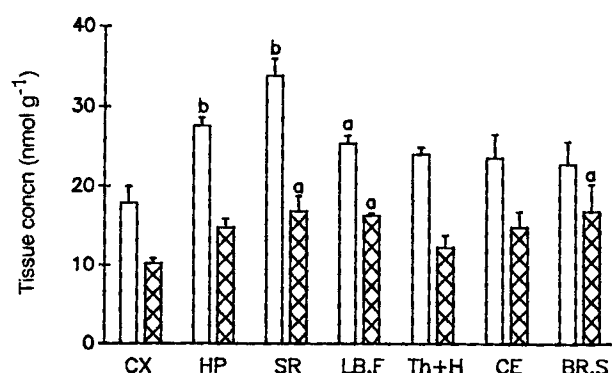

FIG. 1. Imipramine and desipramine levels (nmol (g tissue)$^{-1}$) in different regions of the rat brain 30 min (fast-disposition phase) after administration of imipramine (single dose of 20 mg kg^{-1} i.p.). The results are presented as the mean of 5 rats + s.e.m. a—$P < 0·05$; b—$P < 0·001$ as compared with the level of imipramine or desipramine in the cortex (analysis of variance followed by Dunnet's test). CX—cortex, HP—hippocampi, SR—striatum, LB.F—limbic forebrain, TH + H—thalamus + hypothalamus, CE—cerebellum, BR.S—brain stem. □—imipramine; ⊠—desipramine.

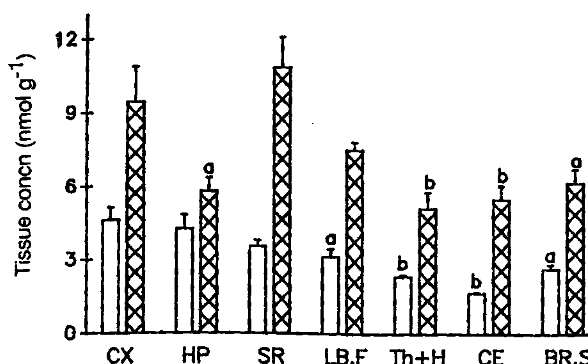

FIG. 2. Imipramine and desipramine levels (nmol (g tissue)$^{-1}$) in different regions of the rat brain 4 h (slow-disposition phase) after administration of imipramine (single dose of 20 mg kg^{-1} i.p.). The results are presented as the mean of 4-5 rats + s.e.m. For further information see Fig. 1.

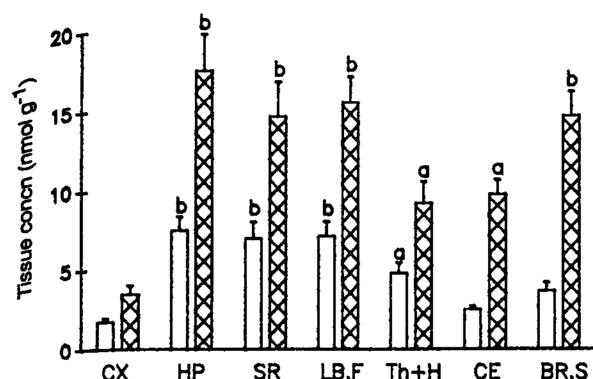

FIG. 3. Imipramine and desipramine levels (nmol (g tissue)$^{-1}$) in different regions of the rat brain 8 h (elimination phase under steady-state conditions) after administration of the last dose of imipramine given to rats for two weeks (daily dose of 20 mg kg^{-1} i.p.). The results are presented as the mean of 4-5 rats + s.e.m. For further information see Fig. 1.

Table 2. Distribution of specific [^{3}H]desipramine binding sites in different regions of the rat brain after single (20 mg kg^{-1} i.p.) (A) or multiple (14 × 20 mg kg^{-1} i.p.) (B) administration of imipramine. The B_{max} values were calculated by Scatchard analysis and are given as the mean ± s.e.m. The number of separate Scatchard plots is given in parentheses, each of 5 concentrations of [^{3}H]desipramine determined in duplicate. $^aP < 0{\cdot}05$ in comparison with the cortex and hippocampi; $^bP < 0{\cdot}05$ in comparison with the corresponding control value (analysis of variance followed by Dunnet's test).

	B_{max} (fmol (mg protein)$^{-1}$)		
Region	Control	A	B
Cortex	205·00 ± 31·33 (5)	190·72 ± 23·15 (5)	121·45 ± 14·56[b] (7)
Hippocampi	239·80 ± 22·87 (4)	217·09 ± 32·67 (5)	139·54 ± 16·22[b] (5)
Cerebellum	188·33 ± 38·61 (5)	154·07 ± 19·03 (5)	142·89 ± 21·13 (6)
Striatum	127·45 ± 25·82[a] (3)	131·67 ± 10·40[a] (4)	92·34 ± 10·98 (4)

Table 3. The K_d values of specific [^{3}H]desipramine binding sites, calculated by Scatchard analysis in different regions of the rat brain after single (20 mg kg^{-1} i.p.) (A) or multiple (14 × 20 mg kg^{-1} i.p.) (B) administration of imipramine. The number of Scatchard plots is given in parentheses. For further information see Table 2.

	K_d (nM)		
Region	Control	A	B
Cortex	1·84 ± 0·40 (5)	2·09 ± 0·32 (5)	2·12 ± 0·35 (5)
Hippocampi	1·69 ± 0·31 (4)	1·85 ± 0·42 (5)	1·79 ± 0·29 (5)
Cerebellum	2·00 ± 0·51 (5)	1·90 ± 0·18 (5)	2·49 ± 0·32 (6)
Striatum	2·31 ± 0·39 (3)	2·09 ± 0·41 (4)	2·19 ± 0·21 (4)

not differ significantly, while the B_{max} values for the striatum were significantly lower than those for the cortex or hippocampi (Table 2). The binding affinity (K_d) in control animals was similar in all the investigated areas and amounted to ca 2·00 nM (Table 3).

When given to rats at a single dose of 20 mg kg^{-1} i.p. imipramine did not change the number of [^{3}H]desipramine specific binding sites (B_{max}) or the K_d value in particular brain regions, when compared with the control (Tables 2, 3).

Chronic treatment of rats with imipramine (14 × 20 mg kg^{-1} i.p.) led to a significant decrease in the number of [^{3}H]desipramine specific binding sites in the cortex and hippocampi, when compared with the control. The B_{max} value for the striatum and cerebellum was also diminished (by 25 and 28%, respectively) but not significantly (Table 2). Chronic administration of imipramine to rats did not affect the affinity (K_d) of binding (Table 3).

Discussion

As indicated by the present results, imipramine and desipramine accumulated in the rat CNS and were unevenly distributed within the brain at 30 min and 4 and 8 h intervals after administration of imipramine in a single or multiple dose. The regional distribution of peripherally administered drugs in the CNS may be partly due to local differences in the cerebral blood flow, lipophilicity of the substances, lipid content in different brain areas and the permeability of various biological barriers. The cerebral blood flow, though different in various brain regions (Sakurada et al 1978), should affect all substances to the same extent, provided that the blood supply itself is not influenced by them.

At the fast-disposition phase, 30 min after a single administration of imipramine, deep cerebral structures (hippocampi and striatum) accumulated drug and metabolite to a higher extent than the cortex; however, the ratio of desipramine to imipramine in those and other areas investigated (except the brain stem) was similar. This finding might indicate that though drugs entered particular brain areas at different rates, there were no regional differences in their affinity for the individual tissues shortly after their administration (the affinity is regarded as a function of drug lipophilicity and lipid content in the particular brain areas). Therefore in the fast-disposition phase the cerebral blood flow and permeability of barriers, rather than lipophilicity of the drugs and lipid content in the areas, determined the regional distribution of the drugs within the rat brain.

In the slow-disposition phase the ratio of desipramine to imipramine was more diversified in particular brain regions when compared with the fast-disposition phase; this phenomenon might be due to a diverse affinity of both drugs for different brain areas because of the varying lipid content of these regions. If the distribution of the drugs is caused just by lipophilicity, their accumulation in particular regions of the rat CNS should be proportional to the lipid level in those areas. However, their distribution did not follow the quantitative and qualitative lipid content in particular brain regions (Tayyaba & Hasan 1985) in the slow-disposition phase (a relatively high level of both drugs in the cortex in comparison with the brain stem or hippocampi).

In the elimination phase under steady-state conditions relatively high levels of the drugs were found in the hippocampi, striatum, limbic forebrain and brain stem, i.e. in the areas that contain more lipids than the cortex (Tayyaba & Hasan 1985). This finding might indicate that in the elimination phase under steady-state conditions the lipid content in the region and lipophilicity of the substances are

crucial factors which determine the drugs' regional cerebral distribution. Their higher accumulation in the elimination phase compared with the slow disposition phase in all the regions investigated (except the cortex) may be due not only to the cumulation of the subsequent doses of imipramine, but also to the changes of lipid content and composition in particular areas, induced by prolonged exposure of the tissue to the drugs. After chronic administration of tricyclic antidepressants excessive phospholipid accumulation and decrease in cholesterol has been noted in cells of various species (Lüllman-Rauch 1979).

The slow-disposition phase and elimination phase under steady-state conditions were characterized by a relatively higher level of metabolite in all the areas investigated, the ratio increasing approximately 5 times in comparison with the fast-disposition phase. This was probably due to a higher lipophilicity of desipramine.

Both drug and metabolite inhibited monoamine uptake in-vitro at concentrations at least an order of magnitude lower (Moret et al 1985) than those found in our pharmacokinetic study (10 nM and 10 μM, respectively). If these agents are essentially sequestered in the lipid phase of rat CNS as has been suggested, only a small amount of drug is available at the synaptic cleft. Therefore, for the inhibition of monoamine uptake in-vivo a much higher concentration of antidepressant is required than that needed in-vitro. Indeed, Moret et al (1985) found that only high doses of tricyclic drugs (at least 10 mg kg^{-1}) affected the uptake in-vivo.

The analysis of binding data indicated that [^{3}H]desipramine specific binding sites were distributed more or less uniformly in the cortex, hippocampi and cerebellum of control animals (the differences among these areas were not statistically significant), while the number of [^{3}H]desipramine specific binding sites in the striatum was significantly lower than those in the other regions investigated. This finding is in accordance with the suggestion of Raisman et al (1982) and Biegon & Rainbow (1983) that [^{3}H]desipramine specific binding sites are associated with neuronal uptake of noradrenaline. Unlike the cortex, hippocampi or cerebellum, the striatum lacks noradrenergic innervation.

Chronic treatment of rats with imipramine led to a decrease in [^{3}H]desipramine specific binding sites in all the investigated regions (significant in the cortex and hippocampi). It has been reported (Wesemann et al 1988; Melzacka et al 1988) that imipramine alters the cortical membrane fluidity in in-vitro and ex-vivo studies, and that chronic treatment of rats with imipramine affects the membrane architecture, as those membranes become more resistant to the fluidizing effect of imipramine than the cortical membranes of control rats or of rats treated acutely with the drug. Changes in physicochemical properties of the membrane, induced by long-lasting exposure of the tissues to drug or metabolites, may therefore lead to internalization of [^{3}H]desipramine specific binding sites or to their dissociation from the membrane into the biophase. However, down-regulation of [^{3}H]desipramine specific binding sites after chronic treatment with imipramine due to the presence of the trace amount of metabolite in the membrane preparation cannot be excluded. Raisman et al (1982) showed that the binding of [^{3}H]desipramine is selectively inhibited by drugs which inhibit the uptake of noradrenaline, including desipramine, and our pharmacokinetic data (Daniel et al 1981) indicated that 24 h after the last dose of imipramine given chronically to rats, desipramine concentration in the rat brain was ca 1 μg g^{-1} (approx. 3 μM).

The comparison of pharmacokinetic and binding data does not indicate a relationship between the regional distribution of desipramine and the regional distribution of [^{3}H]desipramine binding sites within the brain of animals treated acutely or chronically with imipramine. Desipramine accumulated to a greater extent in the striatum than it did in the cortex at all the times investigated, though the number of [^{3}H]desipramine specific binding sites in the striatum was significantly lower than in the other brain areas.

Nor could we demonstrate a relationship between the regional distribution of drug and metabolite and the density of NA and 5-HT uptake sites within rat CNS. For example, the hypothalamus is an area characterized by a high density of NA terminals but the level of desipramine in this region was similar to the level in cerebellum although the density of NA terminals in the cerebellum is much lower than in hypothalamus (Bjorklund & Hokfelt 1984). Imipramine levels in hypothalamus, cerebellum and brain stem were similar though the latter region possessed a higher density of 5-HT terminals than cerebellum or hypothalamus (Bjorklund et al 1984).

At present it is difficult to determine and understand the physiological function of [^{3}H]desipramine specific binding sites in the rat CNS and to elucidate the role played by their down-regulation in the pharmacology of imipramine after chronic treatment with this antidepressant. No information is yet available on the persistence of the down-regulation of [^{3}H]desipramine binding after withdrawal of the drug. Briley et al (1982) found that down-regulation of specific [^{3}H]imipramine binding sites in the cat CNS, induced by prolonged administration of imipramine, was relatively short-lasting and disappeared within 88 h after the last dose of imipramine. If the specific [^{3}H]desipramine binding sites behave like [^{3}H]imipramine sites, they would only play a regulatory function, if any, which is not directly connected with the therapeutic effect of imipramine, providing the specific [^{3}H]desipramine binding sites are present in the human brain and a short-lasting down-regulation of these sites occurs after chronic treatment with imipramine.

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