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Localization of MPP^+ binding sites in the brain of various mammalian species

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Summary. The distribution and density of ^{3}H-MPP^+ binding sites were studied by in vitro quantitative autoradiography in the brain of the mouse, rat and monkey. The highest levels of ^{3}H-MPP^+ specific binding were observed in rat brain. The substantia nigra in rat and monkey, and the anterior caudate-putamen formation in mouse and monkey showed the lowest density of autoradiographic grains. The presence of a relatively high density of MPP^+ sites in the hippocampus of all species studied could be of interest to explain some effects of MPTP administration on convulsions caused by chemoconvulsants.

The finding of a 60–70% reduction of ^{3}H-MPP^+ binding sites in the rat caudate-putamen, on the side of quinolinic acid infusion and no changes after 6-hydroxydopamine lesion of dopaminergic nigrostriatal neurons suggests the presence of these sites mainly on striatal cells.

The results suggest that the distribution of MPP^+ binding sites in brain would not seem to be related to MPTP toxicity.

Keywords: MPP^+, binding sites, autoradiography mammalian brain, dopamine, neurotoxicity.

Introduction

Systemic exposure to 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) produces Parkinson's disease-like symptoms in man and in primates (Burns et al., 1983; Davis et al., 1979; Langston et al., 1983). The toxicity of MPTP may result from its biotransformation to 1-methyl-4-phenyl-2, 3-dihydropyridinium ion (MPP^+) by type B monoamine oxidase (MAO-B) (Chiba et al., 1984; Fuller and Hemrick-Luecke, 1985). Pretreatment of mice and monkeys with selective MAO-B inhibitors prevents the neurotoxic action of MPTP (Cohen et al., 1985; Heikkila et al., 1984).

MPP^+ has been identified in monkey and mouse brain after MPTP treatment (Markey et al., 1984) and is toxic when administered directly into the rat neostriatum (Bradbury et al., 1986).

Since MPP^+ appears to be responsible for the damage to the dopaminergic neurons, various authors characterized ^{3}H-MPP^+ binding sites in mouse brain membranes (D'Amato et al., 1986; Del Zompo et al., 1986a, 1990). Apparently, these are pharmacologically different from ^{3}H-MPTP sites in mouse which closely correlate to MAO-B (Bocchetta et al., 1985; Del Zompo et al., 1986b; Rainbow et al., 1985).

In fact neuromelanin in primate and MAO-A in mouse brains have recently been shown to bind MPP^+ and their role as an intracellular depot for the toxic metabolite in dopaminergic neurons has been suggested (D'Amato et al., 1986; Del Zompo et al., 1990).

Considering both the involvement of the dopaminergic system, particularly the nigrostriatal part, and the role of MPP^+ in MPTP neurotoxicity, it could be of interest to characterize the location of ^{3}H-MPP^+ binding sites in brain with particular regard to the dopaminergic system.

The present study was designed to autoradiographically investigate the distribution of ^{3}H-MPP^+ binding sites in the brain of 3 mammalian species, such as the mouse and the monkey, wich are MPTP-sensitive, and the rat, which is considered insensitive. Moreover, to further define the cellular location of MPP^+ binding sites in the nigrostriatal system, we studied the binding of ^{3}H-MPP^+ in rats lesioned by different specific neurotoxins. 6-hydroxydopamine hydrochloride (6-OHDA) was used to lesion nigrostriatal neurons and quinolinic acid to cause an axon sparing lesion in rat nucleus-caudatus (CPu) (Schwarcz et al., 1983).

Material and methods

Animals

The species investigated in this study included male Sprague-Dawley rats (270–300 g), male Swiss-Webster mice (22–25 g), and adult female Common Marmoset (Callithrix Jacchus) monkey (350 g). For the distribution study we used four rats, four mice and one monkey. For the study with 6-OHDA we used five rats; the same number of rats were involved in the quinolinic-acid study.

Autoradiography

Brains were rapidly removed from the skull after decapitation, coated with plastic embedding medium (OCT compound, Lab-Tek products) onto microtome chucks and rapidly frozen. Consecutive coronal brain sections (20 μm) were cut on a motor driven cryostat (Bright Instruments Co., Ltd) and thaw-mounted onto chrome alum gelatin-coated glass slides. They were then air-dried at room temperature and stored at − 20 °C until used.

Consecutive slide-mounted sections were processed for ^{3}H-MPP^+ binding. Sections were preincubated in 50 mM Tris-HCL buffer pH 7.4 for 5 min and incubated for 45 min at 4 °C in the same buffer containing 15 nM ^{3}H-MPP^+ (88.4 Ci/mmol, NEN, Boston, MA). Specific binding is defined as the difference between total binding and binding in the presence

of 10 μM unlabeled MPP^+ (R.B.I., Wayland, MA, U.S.A.). At the end of the incubation, sections were washed 2 × 5 min in ice-cold 50 mM Tris-HCl buffer pH 7.4. The sections were then dried under a stream of cold air and stored overnight in a dessicated slide box at 4 °C. The dried sections were placed in light-proof cassettes and co-exposed to tritium-sensitive film (LKB Ultrafilm 3H, Sweden) with tritiated standards (Amersham, microscales) for 3–5 weeks. The film was developed at room temperature, fixed, rinsed in water and allowed to dry. Quantitation of autoradiographs was by computerized densitometry (ASBA Wildt Leitz AG, Basel).

The anatomical structures were identified according to the Atlas by Paxinos and Watson (1982), for the rat, the stereotaxic atlas by Slotnick and Leonard (1975) for the mice and the Atlas by Stephan et al. (1980) for the common Marmoset.

Animal surgery

Two groups of rats were anaesthetized with choral hydrate (400 mg/kg i.p.), positioned in a David Kopf stereotaxic apparatus and injected either with 6-OHDA (Sigma Chemical Co., St Louis, MO) or with quinolinic acid (Sigma Chemical Co., St Louis, MO). These rats were initially pretreated with desmethyl-imipramine (25 mg/kg i.p.) to avoid noradrenergic neurons damage.

6-OHDA hydrochloride (8 μg in 4 μl of saline containing 0.05% ascorbic acid) was prepared immediately prior to use and was injected into the left medial forebrain bundle (MFB) at coordinates A 2.2, L 1.5, V 7.9 (Pellegrino et al., 1979) through a stainless steel cannula of 0.3 mm external diameter. The right MFB was injected with the vehicle as control. Fourteen days post-lesion all rats were challenged with apomorphine hydrochloride (0.1 mg/kg s.c.) and subsequent rotational behaviour was noted. Only rats showing a tight head-to-tail contralateral posture and high intensity circling (> 200 turns in 60 min) were killed and used for the assay 30 days after surgery.

Quinolinic acid (150 nmoles in 1 μl of sodium phosphate buffer 0.1 M, pH 7.4) was injected in the left CPu at coordinates A 2.4, L 2.6, V 5. The rats were tested 3 days later with apomorphine hydrochloride (0.5 mg/kg s.c.) and only rats showing a tight head-to-tail ipsilateral posture and high intensity circling (> 200 turns in 60 min) were killed and used for the assay 7 days after surgery.

Results

Regional distribution of ^{3}H-MPP^+ binding sites in the brain of the various species studied

The computer-assisted image analysis of autoradiographs prepared from various sections of brain revealed a heterogeneous distribution of ^{3}H-MPP^+ binding sites, with a difference in group mean values which was most significant for the rat and extremely significant for the mouse (Table 1).

The distribution and relative densities of high affinity MPP^+ binding sites of the monkey is shown in Table 2.

Regarding the areas examined in each species, the highest levels of ^{3}H-MPP^+ specific binding were observed, respectively, in the nucleus accumbens and hippocampus of the rat, in the locus coeruleus of the mouse and in the thalamus, posterior putamen and nucleus caudate (CPu) of the monkey.

A statistically significant difference between rat and mouse was observed in the nucleus accumbens whereas in other brain areas such as hippocampus

Table 1. Distribution and relative densities of high affinity MPP^+ binding sites in the mouse and rat brain

Neuroanatomical structure	Rat[a]	Mouse[b]
Nucleus accumbens	118 ± 13	35 ± 12[c]
Nucleus caudatus (anterior level)	96 ± 21	27 ± 7[c]
Nucleus caudatus (posterior level)	99 ± 18	67 ± 14[d]
Corpus callosum	27 ± 5	17 ± 2
Hippocampus	109 ± 23	70 ± 7
Substantia nigra	46 ± 8	72 ± 11
Locus coeruleus	N. M.*	109 ± 11

Coronal sections were incubated with 15 nM of ^{3}H-MPP^+. Non specific binding was defined by 10 μM of unlabeled MPP^+ and was substracted from all density readings.

Specific bindings values (fmol/mg tissue) are means ± S.E.M. of 4 rats , 4 mice. **NM* not measured. Significantly different using ANOVA test: [a] among the group means, $p < 0.005$; [b] among the group means, $p < 0.001$.

Significantly different using unpaired Student's t-test: [c] from the same area in the rat, $p < 0.05$; [d] from mouse CPu anterior level: $p < 0.05$

Table 2. Distribution and relative densities of high affinity MPP^+ bindings sites in the monkey brain

Neuroanatomical structure	Specific bound
Nucleus caudatus (anterior level)	36 ± 3
Nucleus caudatus (posterior level)	53 ± 12
Putamen (anterior level)	38 ± 7
Putamen (posterior level)	60 ± 9
Internal capsule	17 ± 5
Globus pallidus	17 ± 7
Thalamus, pulvinar	76 ± 13
Hippocampus	41 ± 6
Substantia nigra	28 ± 5
Entorhinal cortex	40 ± 7
Cerebellum	36 ± 1

Coronal sections were incubated with 15 nM of ^{3}H-MPP^+. Non specific binding was defined by 10 μM of unlabeled MPP^+ and was substracted from all density readings. Results are means ± S.E.M. of 8 readings from 1 monkey

and substantia nigra the difference was not significant (Table 1). Another significant variation between rat and mouse in the density of binding sites was found in the CPu. The values of the density of MPP^+ binding sites were very similar between the anterior and posterior level of CPu in the rat whereas the mouse showed a statistically significant difference with a marked and significative anterior-posterior gradient (Table 1) and without any apparent gradient

along the lateral-medial axis of the caudate-putamen formation (data not shown).

Marmoset monkey presented the highest levels of ^{3}H-MPP$^+$ specific binding in the thalamus, posterior putamen and nucleus caudatus while the lower densities of these sites were observed in substantia nigra and globus pallidus. Moreover, the values of the density of MPP$^+$ binding sites between the anterior and posterior level of CPu showed a difference with an anterior-posterior gradient (Table 2).

Relatively high density of ^{3}H-MPP$^+$ binding sites was found in the caudate-putamen of all species. The distribution of ^{3}H-MPP$^+$ binding sites at the level of the caudate-putamen in monkey and rat is shown in Fig. 1. It is evident that within the striatum the distribution of grains in punctate with islands of high and low density.

Non-specific binding ranged from 10 to 15% depending on the area and species examined.

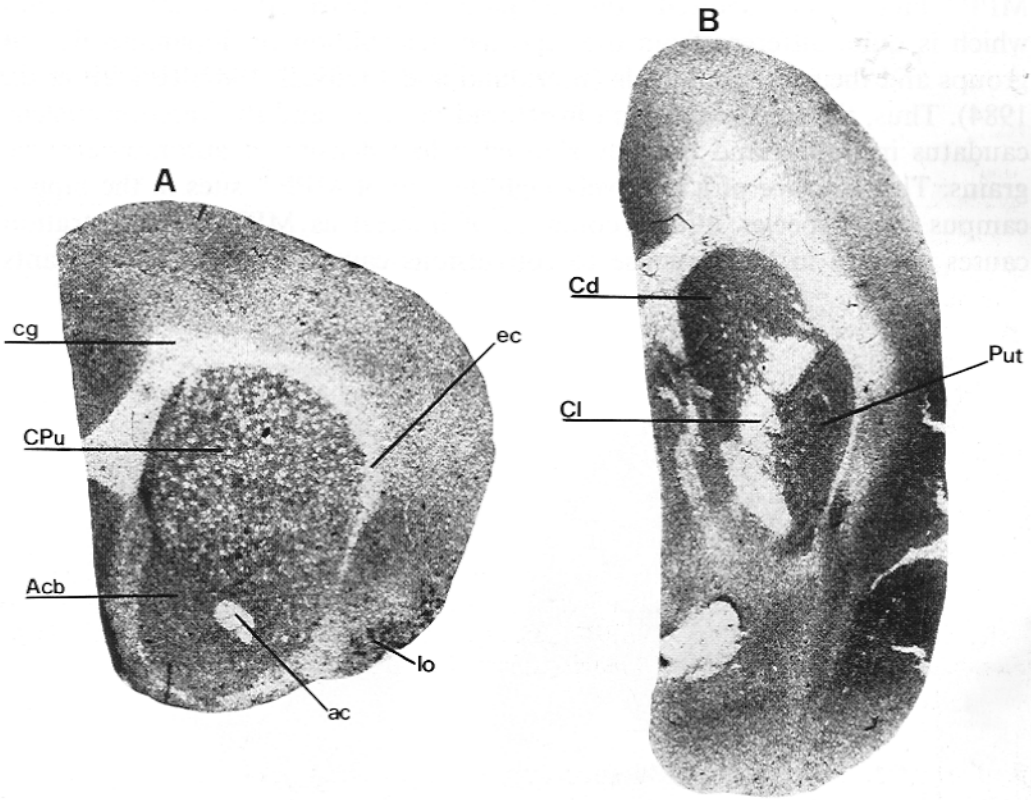

Fig. 1. Distribution of ^{3}H-MPP$^+$ binding sites in section at the level of caudate-putamen in rat (**A**) and monkey (**B**). Brain sections were incubated for 45 min. at 4 °C in 50 mM TRIS-HC1 buffer pH 7.4, washed 2 × 5 min, dried and apposed against tritium sensitive film. *ac* anterior commissure; *Acb* accumbens nucleus; *cg* cingulum; *CPu* nucleus caudatus; *ec* external capsule; *lo* lacteral olfactory tract; *Cd* caudate; *CI* internal capsule; *Put* Putamen

Effect of lesions on ^{3}H-MPP$^+$ binding in caudate-putamen and substantia nigra in rat

The 6-OHDA lesion of nigrostriatal pathway did not modify the ^{3}H-MPP$^+$ binding in CPu area (intact side: 91 ± 16 fmol/mg tissue; lesioned side: 86 ± 18 fmol/mg tissue) as shown in Fig. 2, nor in substantia nigra (intact side: 42 ± 5 fmol/mg tissue; lesioned side: 47 ± 8 fmol/mg tissue).

The quinolinic acid lesion of the left CPu significantly reduced (60–70%) the ^{3}H-MPP$^+$ density respect to the intact side (lesioned side: 42 ± 3 fmol/mg tissue; intact side: 100 ± 8 fmol/mg tissue; $p < 0.001$, $n = 5$). On the contrary, this lesion did not modify the ^{3}H-MPP$^+$ binding in the substantia nigra. Figure 3 shows the marked decrease of grains in the lesioned CPu respect to the intact side.

Discussion

The distribution of ^{3}H-MPP$^+$ binding sites was determined in rat, mouse and monkey brain using autoradiographic techniques. In all species studied the ^{3}H-MPP$^+$ binding sites showed a distinct pattern of distribution within the brain which is quite different from the reported distribution of dopaminergic cell groups and their terminal fields (Bjorklund and Lindvall, 1984; Hokfelt et al., 1984). Thus, the substantia nigra in rat and monkey, and the anterior nucleus caudatus in mouse and monkey showed a low density of autoradiographic grains. The presence of a relatively high density of MPP$^+$ sites in the hippocampus of all species studied could be of interest as MPTP administration causes changes in the response to convulsions caused by chemoconvulsants

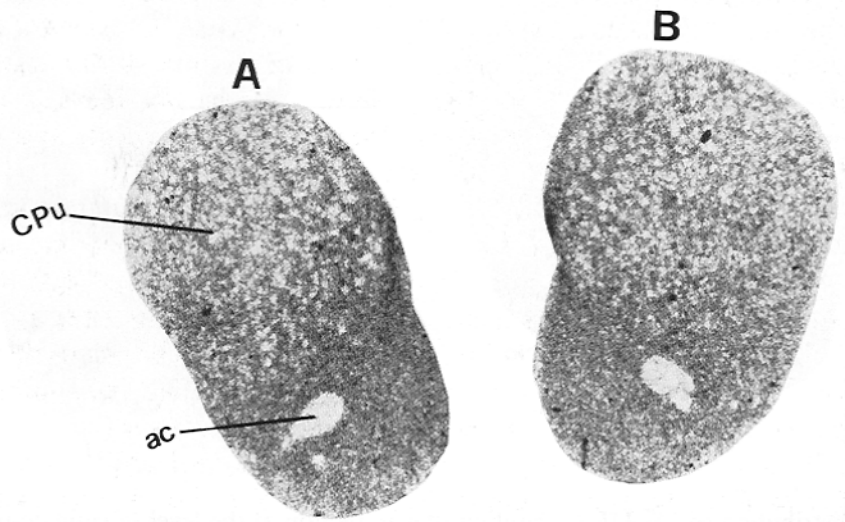

Fig. 2. ^{3}H-MPP$^+$ binding sites in nucleus caudatus of rat lesioned with 6-OHDA (8 µg in 4 µl of saline containing 0.05% ascorbic acid) injected in the medial forebrain bundle at coordinates A 2.2, L 1.5, V 7.9. **A** intact side; **B** lesioned side. *CPu* nucleus caudatus; *ac* anterior commissure; *Acb* Accumbens nucleus

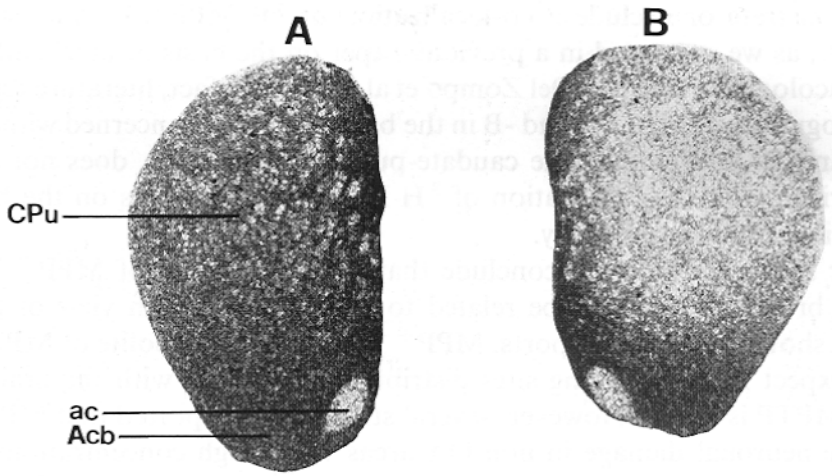

Fig. 3. ^{3}H-MPP^{+} binding sites in nucleus caudatus of rat lesioned with quinolinic acid (150 nmoles in 1 µl of sodium phosphate buffer 0.1 M, pH 7.4) injected in CPu at coordinates A 2.4, L 2.6, V 5. **A** intact side; **B** lesioned side. *CPu* caudate putamen; *ac* anterior commissure; *Acb* Accumbens nucleus

(Fariello et al., 1987). Particularly, acutely administered MPTP causes seizures at high doses and enhanced maximal electroshock seizures at lower doses (Van Ness et al., 1989). In order to explain these effects we suggest further evaluation of the non dopaminergic and non toxic-related action of MPP^{+}.

A further aim of the present study was to investigate the topography of ^{3}H-MPP^{+} binding sites within the nucleus caudatus. In all species studied, a tendency towards a greater density of binding sites was found in the ventral part of the nucleus. A caudal to rostral decrease in the concentrations of MPP^{+} sites was also found in autoradiographs of coronal sections of the mouse and the monkey. The gradients of ^{3}H-MPP^{+} binding site density does not seem to correspond to regional variations in the density of DA receptors and uptake sites (Scatton et al., 1985, 1986; Tassin et al., 1976).

6-OHDA is a neurotoxin which preferentially damages catecholaminergic neurons (Javoy et al., 1976; Jonsson, 1983), while quinolinic acid injected into rat CPu produces a local, axon sparing lesion (Schwarcz et al., 1983).

The finding of a 60–70% reduction of ^{3}H-MPP^{+} binding sites on the rat CPu, on the side of quinolinic acid infusion suggests the presence of these sites mainly on striatal cells. The lack of change in MPP^{+} binding site number after 6-OHDA induced denervation further supports this hypothesis.

The differential effect of the two chemical lesions on MPP^{+} binding sites may be related to the actual cellular location of this site. In fact this study provides evidence that MPP^{+} binding sites are mainly located postsynaptically to the nigrostriatal terminals, even though the precise identity of the striatal neuron bearing these MPP^{+} binding sites remains unknown.

Further investigation, using autoradiographic technique, is required in order

to demonstrate or exclude a co-localization of ^{3}H-MPP$^+$ binding sites and MAO-A, as we suggested in a previous paper on the basis of biochemical and pharmacological evidence (Del Zompo et al., 1990). In fact, literature regarding the topography of MAO-A and -B in the brain is mainly concerned with human tissue and, with regard to the caudate-putamen formation, does not allow a comparison with the localization of ^{3}H-MPP$^+$ binding sites on the brain of all species tested in our study.

Our study allows us to conclude that the distribution of MPP$^+$ binding sites in brain seems not to be related to MPTP toxicity. In view of the fact that, as shown by several reports, MPP$^+$ is the toxic metabolite of MPTP, one could expect MPP$^+$ binding sites distribution to match with the brain areas where MPTP is found. However, several studies have reported that MPP$^+$ can produce neuronal damage in non-DA areas when high concentrations of the toxin are used (Sun et al., 1988; Namura et al., 1987) and indeed other factors such as MPP$^+$ uptake (Javitch et al., 1985) and long-term storage of subtoxic amounts of MPP$^+$ within the neurons (Herkenham et al., 1991) have been shown to be determinant for its toxicity. Therefore, the results obtained in our study, while adding a new issue by showing the distribution of MPP$^+$ binding sites in different mammalian species, also supported the current view that MPP$^+$-induced DA toxicity is not merely dependent on the presence of these binding sites in DA rich areas, but that other factors should be taken into account in the understanding of the mechanisms causing MPTP-induced neurotoxicity.

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