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Complex I inhibitor effect on the nigral and striatal release of dopamine in the presence and absence of nomifensine

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Abstract

The effect of inhibitors of complex I respiratory chain – 1-methyl-4-phenylpyridinium ion (MPP^+, 10 μM) and rotenone (100 μM) – on the release and metabolism of dopamine was studied by in vivo microdialysis in the striatum and substantia nigra. Both compounds produced a marked increase in the release of dopamine in the striatum and substantia nigra, which was diminished when nomifensine (20 μM) was included in the perfusion fluid. The 3,4-dihydroxyphenylacetic acid (DOPAC) extracellular output was decreased under MPP^+ (10 μM) perfusion in the striatum and substantia nigra, in the presence and in the absence of nomifensine (20 μM). However, perfusion of rotenone (100 μM) increased or had no effect on DOPAC outflow. Homovanillic acid levels were affected in the same way as DOPAC levels, but the changes were always much less pronounced. These results suggest that the neurotoxic action of MPP^+ or rotenone is similar in the striatum and substantia nigra, indicating the importance of the dopamine uptake system in this neurotoxic action of MPP^+ or rotenone, also suggesting that the dopamine uptake system could have low selectivity and also transports other substances such as rotenone.

Keywords: Dopamine release; MPP^+ (1-methyl-4-phenylpyridinium); Rotenone; Striatum; Substantia nigra; (Rat)

1. Introduction

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a remarkably selective neurotoxin, the administration of which produces extensive destruction of nigrostriatal dopaminergic neurons. The toxicity of this drug is produced through the following sequence: as a hydrophobic molecule, MPTP penetrates the blood-brain barrier relatively easily and is transformed into 1-methyl-4-phenylpyridinium ion (MPP^+) by mitochondrial monoamine oxidase-B (Chiba et al., 1984). The MPP^+ produced is then actively accumulated into dopaminergic neurons via the high-affinity dopamine uptake system (Javitch et al., 1985) and produces its neurotoxic action by inhibition of mitochondrial respiration at the level of complex I of oxidative phosphorylation (Ramsay et al., 1991). This specific selectivity seems to be closely related to the dopamine uptake system.

Rotenone (a classic inhibitor of mitochondrial respiration at complex I (Ernster et al., 1963; Horgan et al., 1968; Gutman et al., 1970)) injected stereotaxically into the median forebrain of rats, produces damage to the nigrostriatal pathway similar to that caused by MPP^+ (Heikkila et al., 1985). Marey-Semper et al. (1993) have recently reported a high sensitivity of striatal dopamine terminals to rotenone.

We have carried out a comparative study of the effect of MPP^+ and rotenone on the striatal and nigral release of dopamine in order to test for similarities or differences between these two compounds, using in vivo microdialysis.

2. Materials and methods

2.1. Animals and drug treatment

Male albino Wistar rats were used for the experiments. The rats were housed in plastic cages (35 × 35 × 40 cm) and allowed free access to food and water. The experiments were carried out in accordance with

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the Guidelines of the European Union Council (86/609/EU) and following the Spanish regulations (BOE 67/8509-12, 1988) for the use of laboratory animals. The experiments carried out in the present study were approved by the Scientific Committee of the University of Sevilla.

The following drugs were dissolved in the perfusion fluid: 1-methyl-4-phenylpyridinium (MPP^+ iodide) and nomifensine maleate (Research Biochemicals, Natick, MA, USA) and rotenone (Sigma Chemical Co., St. Louis, MO, USA).

2.2. Surgery and brain dialysis

Microdialysis in the striatum and substantia nigra was performed with an I-shaped cannula (Santiago and Westerink, 1990). The exposed tip of the dialysis membrane was 4 and 2 mm, respectively. The dialysis tube (i.d.: 0.22 mm; o.d.: 0.31 mm) was prepared from polyacrylonitrile/sodium methalyl sulfonate copolymer (AN 69, Hospal, Bologna, Italy). The in vitro recovery of the membrane (4 mm length, $n = 5$) was: $22.3 \pm 1.8\%$, for dopamine; $31.2 \pm 2.9\%$, for 3,4-dihydroxyphenylacetic acid (DOPAC); $29.5 \pm 3.0\%$, for homovanillic acid (HVA); and $29.2 \pm 2.7\%$, for 5-hydroxyindoleacetic acid (5-HIAA). The probe was implanted into the striatum [A/P 0.6, L/M 2.8, V/D 6.0, from bregma point and dura] and substantia nigra [A/P 3.8, L/M 3.8, V/D 8.7, from interaural line and dura, at an angle of 12°] during general chloral hydrate (400 mg/kg i.p.) and local lidocaine (10% w/v in water) anaesthesia.

The perfusion experiments were carried out 24–48 h after implantation of the probe. Brain dialysis was performed with a fully automated on-line system as has been previously described (Westerink et al., 1987). In brief, two polyethylene tubes (inner diameter = 0.28 mm) were connected to the outlets of the dialysis tube. One tube (45 cm in length) was connected to the perfusion pump, and the other (45 cm in length) to the injection valve of the high performance liquid chromatography (HPLC) apparatus. From the time drugs (MPP^+ or rotenone) were included in the Ringer solution delivered by the perfusion pump to the time when the first sample with drugs was injected onto the column there was a lag time of about 30 min; the data presented are corrected to account for this lag time. With the help of an electronic timer, the injection valve was held in the load position for 15 min, during which the sample loop (40 μl) was filled with dialysate. The valve then switched automatically to the injection position for 15 s. This procedure was repeated every 15 min, which was the time needed to record a complete chromatogram. The striatum and substantia nigra were perfused with a Ringer solution at a flow rate of 3.0 μl/min (perfusor VI, B. Braun, Melsungen, Germany). The composition of the Ringer solution was (in mM): NaCl, 140; KCl, 4.0; $CaCl_2$, 1.2; and $MgCl_2$, 1.0.

When the experiment was finished, the rat was given an overdose of chloral hydrate, and the brain was fixed with 4% paraformaldehyde via intracardiac perfusion. Coronal sections (40 μm thick) were made, and dialysis probe placement was localized according to the atlas of Paxinos and Watson (1986).

2.3. Chemical assays

Dopamine, DOPAC, HVA and 5-HIAA were quantitated by HPLC with electrochemical detection. A Kontron 420 pump was used in conjunction with a glassy carbon electrode set at −780 mV (ANTEC, Netherlands). A Merck Lichrocart cartridge (125 × 4 mm) column filled with Lichrospher reverse-phase C_{18} 5 μM material was used. The mobile phase consisted of a mixture of 0.05 M of sodium acetate, 0.4 mM of 1-octanesulfonic acid, 0.3 mM of Na_2EDTA and 70 ml methanol/l, adjusted to pH 4.1 with acetic acid. The flow rate was 0.8 ml/min and the detection limit for dopamine, DOPAC, HVA and 5-HIAA was 5, 5, 20 and 15 fmol per injection, respectively.

2.4. Expression of results and statistics

The average of the last four stable samples before drug treatment was considered as the control and was defined as 100%. All values given are expressed as percentages of controls, with the exception of Figs. 1A and 2A in which values are expressed as fmol/min. Differences between the average dialysate concentrations of the control and drugs treatment were compared by Kruskal-Wallis analysis of variance by ranks and, where appropriate (H value greater than the 95% confidence level), comparison of the means was carried out using the Mann-Whitney *U*-test. Student's *t*-test was used for comparing the values with and without nomifensine at the same collection time.

3. Results

3.1. Microdialysis basal values

The dopamine basal value was 19.9 ± 1.7 ($n = 12$) and 1.0 ± 0.3 fmol/min ($n = 12$) in the striatum and in the substantia nigra, respectively. Addition of nomifensine in the Ringer solution increased the release of dopamine to 141.7 ± 14.7 ($n = 12$) and 12.5 ± 1.3 fmol/min ($n = 12$) in the striatum and in the substantia nigra, respectively.

The presence of nomifensine in the Ringer solution did not affect the extracellular output of dopamine metabolites and 5-HIAA in the striatum and substantia

nigra. The basal values were as follows (in fmol/min): 1276.4 ± 80.1, for DOPAC; 1141.8 ± 73.0, for HVA; and 958.0 ± 46.1, for 5-HIAA in the striatum ($n = 24$). 68.4 ± 4.7, for DOPAC; 69.2 ± 3.8, for HVA; and 1297.2 ± 59.0, for 5-HIAA in the substantia nigra ($n = 24$).

3.2. Effect of the perfusion of MPP^+ (10 μM) and rotenone (100 μM) on the extracellular output of dopamine, DOPAC, HVA and 5-HIAA in the striatum

Fig. 1A shows the effect of perfusion over 1 h of MPP^+ (10 μM) or rotenone (100 μM) in the presence and in the absence of nomifensine in the striatum. MPP^+, without nomifensine co-perfusion, produced a greater effect on the striatal release of dopamine than did rotenone (dopamine release raised from 22.8 ± 5.5 to 141.2 ± 21.5 and from 18.9 ± 2.6 to 65.2 ± 11.6 fmol/min, respectively, Fig. 1A). The addition of nomifensine (20 μM) to the perfusion fluid markedly reduced the effect produced by MPP^+; the increase in dopamine release was from the basal stimulated release of 120.5 ± 22.6 to 186.0 ± 39.6 fmol/min in the presence of MPP^+ (Fig. 1A). Rotenone perfusion in the presence of nomifensine produced a slow, but persistent, increase in the release of dopamine during and after its perfusion (Fig. 1A).

With respect to DOPAC data, MPP^+ (10 μM) perfusion produced a significant decrease in DOPAC extracellular output, the effect being similar in the absence and in the presence of nomifensine (20 μM). However, rotenone (100 μM) perfusion produced an increase in DOPAC extracellular output which was more significant when nomifensine was included in the perfusion fluid (Fig. 1B). The effect produced by MPP^+ (10 μM) or rotenone (100 μM) perfusion on HVA extracellular output was similar to that found for DOPAC output, but always much less pronounced (Fig. 1C). 5-HIAA levels were not affected by any condition studied (data not shown).

3.3. Effect of the perfusion of MPP^+ (10 μM) and rotenone (100 μM) on the extracellular output of dopamine, DOPAC, HVA and 5-HIAA in the substantia nigra

Perfusion of MPP^+ (10 μM) for 1 h produced a greater increase in the release of dopamine than that produced by perfusion of rotenone (100 μM) in the substantia nigra (Fig. 2A). When nomifensine was added to the perfusion fluid, the effect of MPP^+ (10 μM) and rotenone (100 μM) on the release of dopamine was totally absent (Fig. 2A).

With respect to the DOPAC output, we observed a different effect of the perfusion of MPP^+ (10 μM) compared with the perfusion of rotenone (100 μM).

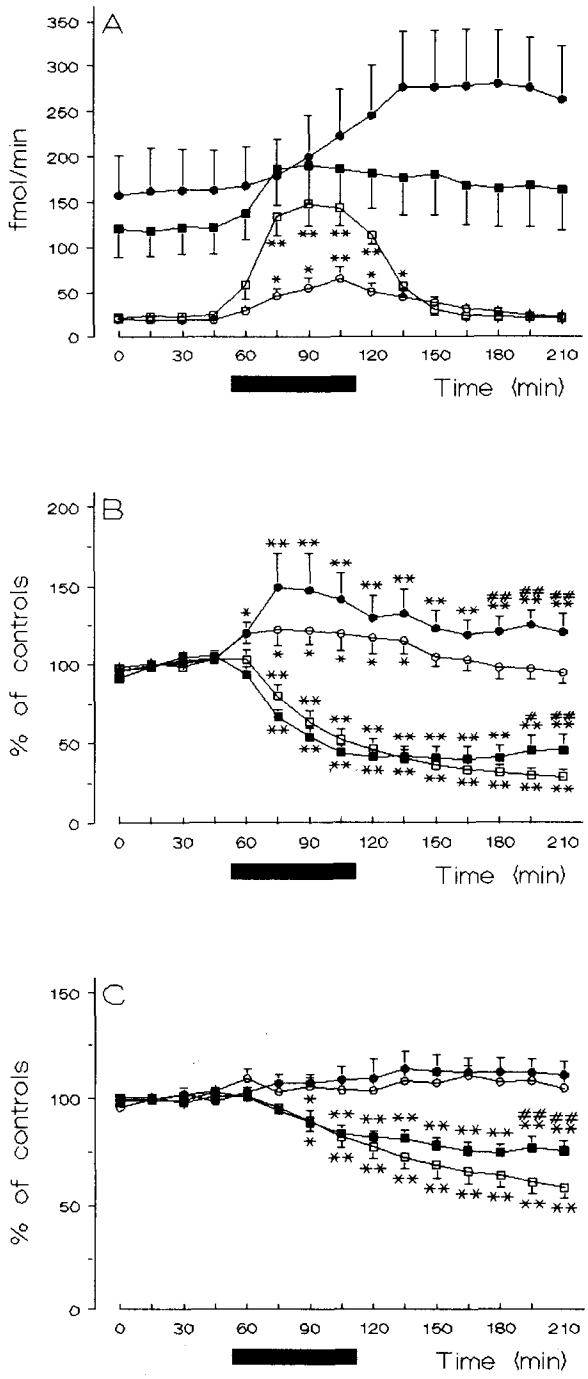

Fig. 1. Effect of perfusion (black bar) of MPP^+ (10 μM, squares) and rotenone (100 μM, circles) on the extracellular output of dopamine (A), DOPAC (B) and HVA (C) in the striatum in the absence (open symbols) and in the presence (filled symbols) of nomifensine (20 μM). The data are mean ± S.E.M. (bars) values ($n = 6$), expressed as percentages of the controls, except in Fig. 1A where they are expressed as fmol/min. Statistical significance: $^{*}P < 0.05$; $^{**}P < 0.01$, compared with the control value (Kruskal-Wallis followed by Mann-Whitney U-test). $^{\#}P < 0.05$; $^{\#\#}P < 0.01$, comparing data without and with nomifensine at the same collection time (Student's t-test).

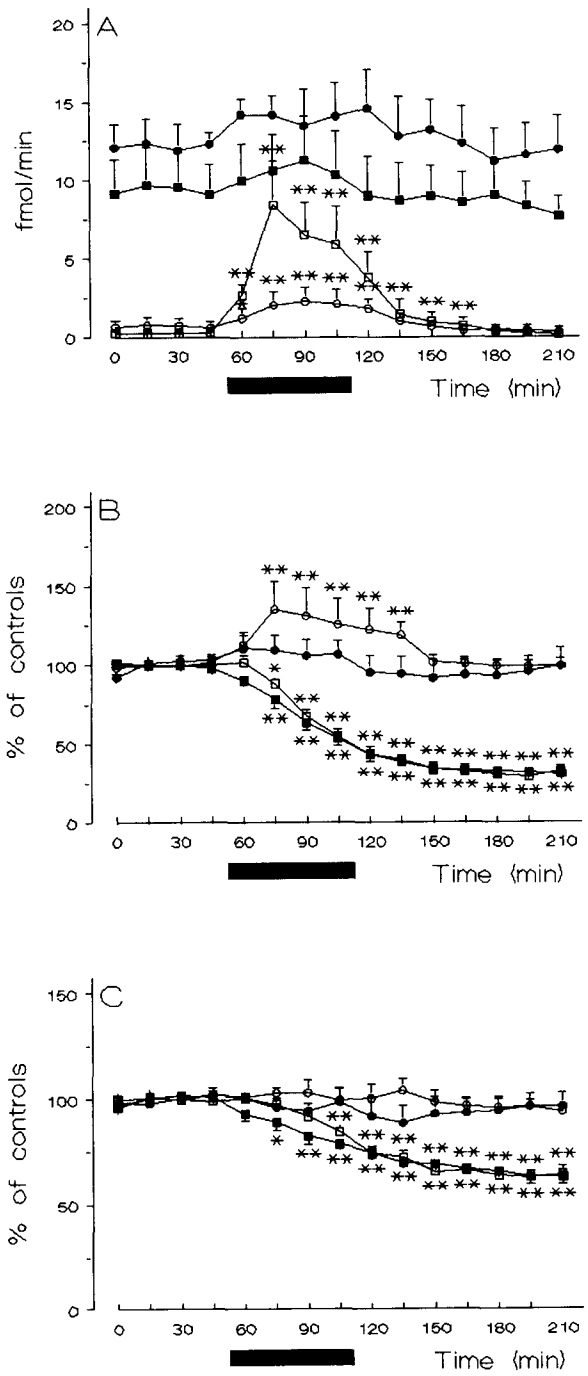

Fig. 2. Effect of perfusion (black bar) of MPP^+ (10 μM, squares) and rotenone (100 μM, circles) on the extracellular output of dopamine (A), DOPAC (B) and HVA (C) in the substantia nigra in the absence (open symbols) and in the presence (filled symbols) of nomifensine (20 μM). The data are mean ± S.E.M. (bars) values ($n = 6$), expressed as percentages of the controls, except in Fig. 2A where they are expressed as fmol/min. Statistical significance: * $P < 0.05$; ** $P < 0.01$, compared with the control value (Kruskal-Wallis followed by Mann-Whitney U-test).

The former produced a decrease in the extracellular output of DOPAC in the presence and in the absence of nomifensine (Fig. 2B). The latter did not modify the level of DOPAC in the presence of nomifensine and increased it when nomifensine was absent (Fig. 2B).

HVA output was affected in the same way as DOPAC output, but the effect was always much less pronounced (Fig. 2C). The 5-HIAA extracellular content was not affected by the perfusion of MPP^+ (10 μM) or rotenone (10 μM) in the presence and in the absence of nomifensine (data not shown).

4. Discussion

MPP^+ (10 μM) perfusion for 1 h in the striatum produced a significant increase in the release of dopamine (about 120 fmol/min), greater than that produced when rotenone (100 μM) was used (about 47 fmol/min). These results show more damage produced by MPP^+ than by rotenone. When perfusion of MPP^+ was carried out in the presence of nomifensine, there was a significant reduction in the effect on dopamine release (the increase in the release of dopamine due to MPP^+ perfusion was about 65.5 fmol/min, a 50% reduction with respect to control MPP^+ perfusion). Using different dopamine uptake inhibitors, the in vivo rank order potency of nomifensine is not as high as that seen for GBR 12909 (Nomikos et al., 1990). These data could account for this only partial inhibition of the MPP^+ effect on dopamine extracellular output. Therefore, we can conclude that the re-uptake mechanism is not changed by MPP^+ and that the sites where dopamine is released are similar under control and experimental (MPP^+ perfusion) conditions. The MPP^+ results are in agreement with other reports that also indicate the importance of the dopamine uptake system in MPTP or MPP^+ toxicity. Low MPP^+ concentrations decrease O_2 consumption in striatal slices but not in hippocampal slices (Martin et al., 1991). The specific uptake and the neurotoxic action of MPP^+ are inhibited or protected by dopamine uptake inhibitors. Treatment of striatal slices with a dopamine uptake inhibitor, mazindol, partially protects against the decline in oxygen consumption produced by low concentrations of MPP^+ (Martin et al., 1991). Dopamine uptake inhibitors protect mice against dopamine loss following treatment with MPTP (Melamed et al., 1985; Mayer et al., 1986). 21-Aminosteroids interact with the dopamine transporter and also protect against MPP^+-induced neurotoxicity (Sanchez-Ramos et al., 1992). The dopamine transporter expression confers cytotoxicity on low doses of MPP^+ and could be specifically antagonized by the catecholamine uptake inhibitor, mazindol (Pifl et al., 1993).

The finding that the effect of rotenone on dopamine release lasted about 1 h when nomifensine was included in the perfusion fluid indicates that rotenone

must be introduced into the dopamine terminals in the striatum by the dopamine uptake system, similarly to MPP^+. However, because of the effect on dopamine release seen after rotenone perfusion, we cannot rule out the possibility that the rotenone effect on dopamine release was due to its directly permeating the plasmatic membrane. These results suggest that the dopamine uptake system, although possibly very active, cannot be very specific, since the dopamine uptake system can transport many others substances. It is known that MPP^+ competes with rotenone for the binding site of the NADH-coenzyme Q segment of the respiratory chain (Horgan et al., 1968; Ramsay et al., 1991), suggesting some similarities could exist between them.

It is important to point out the different effect of MPP^+ and rotenone, as inhibitors of complex I, on the DOPAC and HVA extracellular output. MPP^+ produced a significant reduction of DOPAC output when perfused alone and also with nomifensine. However, in parallel experiments carried out with rotenone, there was always an increase in DOPAC output. In the HVA experiments the results were similar but less significant. These results showed an inhibitory effect of MPP^+ on monoamine oxidase, confirming a previous report (Tipton and Singer, 1993). Therefore, in these conditions, there was a decrease in dopamine metabolism with a consequent decrease in DOPAC output. However, as rotenone did not show the effect seen with MPP^+, the increase in dopamine release led to the increase in its metabolism with the consequent increase in DOPAC output.

Another result which must be noted is the different level of effect of MPP^+ and rotenone. The very high inhibitor effect of rotenone on the NADH-dehydrogenase-complex I in comparison to that of MPP^+ (Horgan et al., 1968) is known. However, in spite of the higher concentration used for rotenone, 100 μM versus 10 μM of MPP^+, the amount of dopamine release produced by MPP^+ was significantly greater than that produced by rotenone. This effect could be related to an unexpectedly greater effect described for MPP^+ as inhibitor of the different pathways studied, i.e. Martin et al. (1991) reported a marked inhibition of MPP^+ on striatum (80% inhibition of oxygen consumption). Similar results were obtained by Sanchez-Ramos et al. (1992) studying cytochrome *b* oxidation. These results are also in agreement with those reported by Scotcher et al. (1990), in which synaptosomal ATP was depleted by concentrations of MPP^+ as low as 10–100 μM, similar to those reached by the toxic metabolite in several areas of the brain of mice and monkeys exposed to MPTP (Irwin and Langston, 1985; Irwin et al., 1987). These results also emphasise the importance of the dopamine uptake system, since it probably actively accumulates MPP^+ into the synaptosomes with the consequent increase in its mitochondrial inhibition. However, taking into account the fact that rotenone has no positive charge, it cannot be accumulated so efficiently into synaptosomes. This result indicates the importance of the positive charge of MPP^+, along with the influence of compounds with a negative charge, such as tetraphenylboran that significantly enhances the inhibitor effect of MPP^+ (Ramsay et al., 1989).

Precisely the same results have been found for substantia nigra. MPP^+ and rotenone increase the release of dopamine. Nomifensine, an inhibitor of the dopamine uptake system, produces protection against the neurotoxic action of both these compounds. The effect of MPP^+ is significantly greater than that of rotenone. These results also suggest the importance of the dopamine uptake system in the neurotoxic action of both compounds in the substantia nigra, and argue against the supposition that the neuronal death produced by MPTP/MPP^+ is a result of their neurotoxic action in the neuronal body reached by retrograde axonal transport. This result is consistent with the fact that intra-substantia nigra pars compacta co-injections of MPTP and L-α-aminoadipic (astroglia-specific toxin) produce protection against MPTP neurotoxicity in a dose-dependent fashion (Takada et al., 1990). Therefore, MPTP is oxidatively converted to MPP^+ by the action of monoamine oxidase B and this enzyme, in the substantia nigra pars compacta, is found specifically in astroglia. MPP^+ must be taken up by the dopamine uptake system to produce the neurotoxic action.

All these results point to the importance of: (a) the dopamine uptake system in the neurotoxic action of MPP^+ and also in the rotenone effect; (b) a positive charge of MPP^+ that could produce its accumulation into the cell with the consequent increase in its inhibitory effect; (c) a low selectivity of the dopamine uptake system that can transport rotenone, which is chemically different. This could amplify the range of compounds, such as environmental toxins, that could be taken by the dopamine uptake system and have a neurotoxic action in dopaminergic neurons.

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