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Protective effect of imidaprilat, a new angiotensin-converting enzyme inhibitor against 1-methyl-4-phenylpyridinium ion-induced ·OH generation in rat striatum

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Abstract

We examined the antioxidant effects of angiotensin-converting enzyme inhibitor on 1-methyl-4-phenylpyridinium ion (MPP^+)-induced hydroxyl radical (·OH) formation in extracellular fluid of rat striatum. Rats were anesthetized and sodium salicylate in Ringer's solution (0.5 nmol μl^{-1} min^{-1}) was infused through a microdialysis probe to detect the generation of ·OH, as reflected by the non-enzymatic formation of 2,3-dihydroxybenzoic acid (DHBA) in the striatum. MPP^+ clearly produced an increase in ·OH formation in a concentration-dependent manner. When imidaprilat was infused in MPP^+-pre-treated animals, the formation of dopamine and 2,3-DHBA significantly decreased, as compared with that in the MPP^+-only-treated group. We compared the ability of two non-SH-containing angiotensin-converting enzyme inhibitors (imidaprilat and enalaprilat) with an SH-containing angiotensin-converting enzyme inhibitor (captopril) to scavenge ·OH. All three angiotensin-converting enzyme inhibitors were able to scavenge ·OH generated by the action of MPP^+. However, the changes produced by captopril and enalaprilat were not significant. When dopamine was administered to the MPP^+-pre-treatment group, a marked elevation was observed, showing a positive linear correlation between dopamine and ·OH formation (2,3-DHBA) in the dialysate. Moreover, when iron (II) was administered to the MPP^+-pre-treatment group, the same results were obtained: a positive linear correlation ($R^2 = 0.989$) between the release of dopamine and 2,3-DHBA ($R^2 = 0.989$) in the dialysate. When corresponding experiments were performed with imidaprilat-pre-treated animals, the level of 2,3-DHBA decreased. These results suggested that angiotensin-converting enzyme inhibitors may protect against MPP^+-induced ·OH formation in the rat striatum.

Keywords: Parkinson's disease; Angiotensin-converting enzyme inhibitor; Free radical; MPP^+ (1-methyl-4-phenylpyridinium ion); Microdialysis

1. Introduction

Angiotensin-converting enzyme (EC 3.4.15.1) is distributed unevenly throughout the human brain (Poth et al., 1975). A high level of angiotensin-converting enzyme activity exists in the basal ganglia, including substantia nigra, globus pallidus, and caudate putamen (Chai et al., 1987). Angiotensin-converting enzyme in the basal ganglia is associated with neurons in the striatum. A neuronal localization, predominantly in synaptic terminals, has been suggested by biochemical and immunochemical studies (Benuck and Marks, 1978). Angiotensin-converting enzyme activity is reported to be altered in regions of postmortem brains from patients with certain neuropsychiatric disorders (Arregui et al., 1977; Zubenko et al., 1985). It is well-known that angiotensin II stimulates the release of dopamine (Brown et al., 1996; Jenkins et al., 1996). The neurochemical mechanisms which underlie the central nervous system-mediated responses following manipulation of the system are poorly understood. Although the role of angiotensin-converting enzyme inhibitors in free radical-scavenging effects are still speculative (Juggi et al., 1993), the activity of captopril is believed to be due to the presence of an SH-group in its structure (Bagchi et al., 1989). However, non-SH-containing angiotensin-converting enzyme inhibitors also provide protection against free radical-induced injury (Mak et al., 1990; Fernandes et al., 1996).

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is oxidized by the B-form of monoamine oxidase (MAO; EC 1.4.3.4) (Chiba et al., 1984; Langston et al., 1984;

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Markey et al., 1984) and is converted to 1-methyl-4 phenylpyridinium ion (MPP^+). MPTP produces a parkinsonian syndrome after its conversion to MPP^+ (Chiba et al., 1984; Markey and Schmuff, 1986). The etiology of Parkinson's disease remains obscure. The cytotoxic hydroxyl radical (·OH) has been implicated in dopamine neurotoxicity caused by MPTP and iron (Youdim et al., 1989; Chiueh et al., 1993). Oxidative stress may be involved in the pathogenesis of idiopathic Parkinson's disease in the nigra (Hirsch et al., 1988; Gerlach et al., 1994). The excessive formation of hydrogen peroxide (H_2O_2) and oxygen-derived free radicals can cause cell damage due to chain reactions of membrane lipid peroxidation and/or alternations in membrane fluidity (Halliwell, 1992). The interaction between angiotensin-converting enzyme inhibitor and MPP^+-induced ·OH formation in the brain is not clear. In the present study, to investigate the antioxidant effects of angiotensin-converting enzyme inhibitor, we examined the protective effect of several angiotensin-converting enzyme inhibitors against MPP^+-induced ·OH formation in extracellular fluid of the rat striatum.

2. Materials and methods

2.1. Animals

Adult male Wistar rats (300–400 g) were housed in an environmentally controlled room (20–25°C, 50–60% of humidity) with food and water available ad libitum for 4 days prior to the experiments. The animals were anesthetized with chloral hydrate (400 mg/kg i.p.; Sigma, St. Louis, MO, USA) and prepared for intracranial microdialysis brain perfusion. This study was approved by the Ethics Committee for Animal Experiments, Oita Medical University.

2.2. Experimental protocol

MPP^+ was purchased from Research Biochemicals, MA, USA Imidaprilat, captopril and enalaprilat were provided by Tanabe Seiyaku, Japan, and captopril was purchased from Sigma (St. Louis, MO, USA). Sodium salicylate and its hydroxylated metabolites were purchased from Sigma. These drugs were dissolved in Ringer's solution containing 147 mM NaCl, 2.3 mM $CaCl_2$ and 4 mM KCl, pH 7.4 for perfusion (1 μl/min) through a microdialysis probe into the striatum.

A guide cannula was implanted stereotaxically on top of the caudate nucleus (stereotaxic coordinates: AP: 1.0, R/L: 2.5, H: −7 mm from dura matter) (Paxinos and Watson, 1982). In preliminary experiments, the recovery rate of 10^{-7} M dopamine was $20.8 \pm 0.9\%$ at a flow rate of 1 μl/min. The drugs were dissolved in Ringer's solution containing 147 mM NaCl, 2.3 mM $CaCl_2$ and 4 mM KCl, pH 7.0 for perfusion (1 μl/min) through a microdialysis probe into the striatum. The microdialysis probe was prewashed with Ringer's solution for at least 30 min prior to stereotaxic implantation in the striatum. Following the scheduled 60-min washout with Ringer's solution, MPP^+ (5 mM or 5 nmol μl^{-1} min^{-1}) was infused for 15 min (total dose: 75 nmol) to evoke the sustained, voltage-regulated, and calcium-dependent release of dopamine. The striatum was then perfused with Ringer's solution (1 μl/min) for at least 60 min.

The ·OH reacts with salicylate to generate 2,3- and 2,5-dihydroxybenzoic acid (DHBA), which can be measured electrochemically in picomole quantities by high-performance liquid chromatography (HPLC) (Floyd et al., 1984; Gerlach et al., 1994; Obata et al., 1994). For trapping ·OH radicals (Floyd et al., 1984; Halliwell et al., 1991) in the striatum, sodium salicylate in Ringer's solution (0.5 nmol μl^{-1} min^{-1}) was infused through a microdialysis probe to detect the generation of ·OH, as reflected by the non-enzymatic formation of 2,3-DHBA. Brain dialysate (1 μl/min) was collected every 15 min in small collecting tubes containing 15 μl of 0.1 N $HClO_4$ to prevent amine oxidation and was assayed immediately for 2,3-DHBA by HPLC with an electrochemical (EC) procedure (Obata and Chiueh, 1992; Smith and Bennett, 1997). In a dose–response experiment, three different concentrations of dopamine (Sigma) (2, 5 and 10 μM) and three different concentrations of ammonium salt (Sigma) (5, 25 and 50 μM) were administered directly through the dialysis probe into the rat brain for 15 min each.

2.3. Analytical procedures

The dialysate samples were immediately injected for analysis into an HPLC-EC equipped with a glassy carbon working electrode (EICOM, Kyoto, Japan) and an analytical reverse-phase Eicompak MA-5ODS column (5 μm, 4.6 × 150 mm; EICOM). The working electrode was set at a detector potential of 0.75 V. Each liter of the mobile phase contained 1.5 g heptane sulfonic acid sodium salt (Sigma), 0.1 g Na_2EDTA, 3 ml triethylamine (Wako) and 125 ml acetonitrile (Wako) dissolved in H_2O. The pH of the solution was adjusted to 2.8 with 3 ml phosphoric acid (Wako).

2.4. Statistical analysis

All values are presented as means ± S.E.M. The significance of differences was determined by using an analysis of variance (ANOVA) with Fisher's post-hoc test. A *P*-value of less than 0.05 was regarded as being statistically significant.

3. Results

After a 60-min washout with pH 7.4 Ringer's solution, MPP^+ (5 mM) was infused into the striatum for 15 min

(total dose: 75 nmol). The present results confirmed that MPP^+ (5 mM) causes sustained dopamine release. In the presence of imidaprilat (50 μM), MPP^+ failed to increase dopamine release (Fig. 1A). In order to trap ·OH radical, the striatum was subsequently perfused with sodium salicylate in pH 7.4 Ringer's solution (0.5 nmol μl^{-1} min^{-1}) for 90 min. Time-dependent changes in the level of the formation of 2,3-DHBA were monitored in the dialysates from the rat brain after MPP^+ (5 mM) treatment. MPP^+ enhanced ·OH generation, as reflected by 2,3-DHBA levels in the brain dialysate. However, in the presence of imidaprilat (50 μM), MPP^+ failed to increase 2,3-DHBA formation (Fig. 2A). Similar experiments were repeated using various concentrations of MPP^+ (1, 5 and 10 mM) in the absence and presence of imidaprilat (50 μM) and the results are summarized in Figs. 1B and 2B. MPP^+ applied at various of concentrations (1, 5 and 10 mM) increased dopamine release and ·OH formation in a concentration-dependent manner. In the presence of imidaprilat (50 μM), MPP^+ failed to increase dopamine release (Fig. 1B) and ·OH formation (Fig. 2B).

We compared the ability of two non-SH-containing angiotensin-converting enzyme inhibitors (imidaprilat and enalaprilat) with that of an SH-containing-angiotensin-converting enzyme inhibitor (catopril) to scavenge ·OH. The

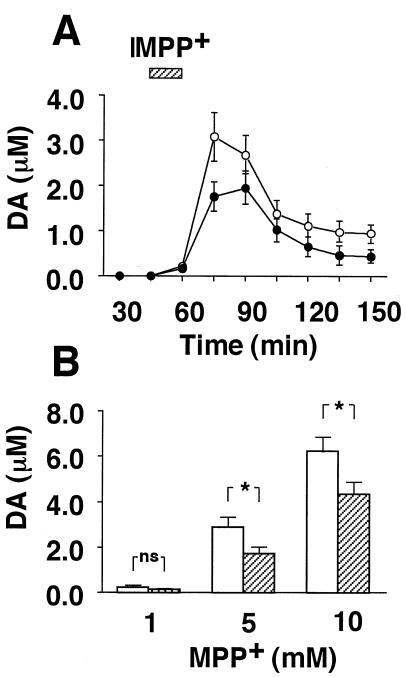

Fig. 1. Effect of MPP^+ (5 mM) on dopamine release in rat striatum. In (A) after a 60-min washout with Ringer's solution pH 7.0, MPP^+ was infused into the striatum for 15 min (closed bar: total dose + 75 nmol) to evoke release of dopamine. Sodium salicylate (open bar: 0.5 nmol μl^{-1} min^{-1}) was infused thereafter for 120 min to trap ·OH radicals. In (B), dopamine levels in MPP^+-only-treated rats (open circle) were compared with those of imidaprilat-treated rats (closed circle). Brain dialysate was collected at 15-min intervals and immediately assayed for dopamine using an HPLC-EC procedure. Values are means ± S.E.M. for six animals.

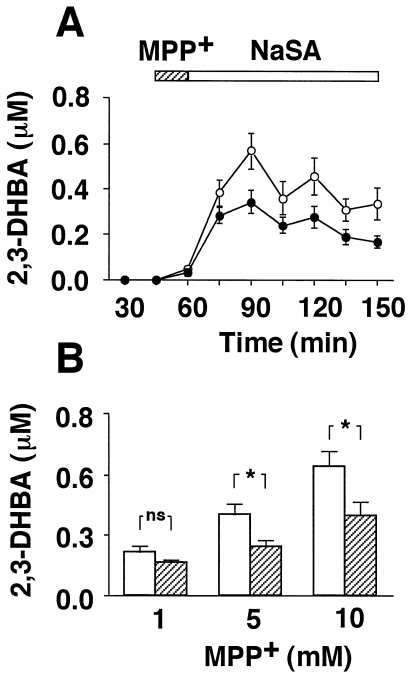

Fig. 2. Concentration-dependent effect of MPP^+ (5 mM) on ·OH formation in the absence and presence of imidaprilat (50 μM). (A) Dopamine release and (B) ·OH formation, measured as 2,3-DHBA, at 30–45 min after application of various concentrations of MPP^+ (as indicated on abscissa) in the non-treated (open column) and treated (closed column) of imidaprilat (50 μM) and given as the value measured just before application of imidaprilat. The microdialysis experiments were performed as described in the text. Each column and vertical bar indicates means ± S.E.M. for six animals; $^*P < 0.05$: significant difference between the data. ns: non-significant.

formation of 2,3-DHBA by MPP^+ progressively decreased with increasing concentrations of captopril, enalapril and imidapril (Fig. 3). Imidaprilat significantly decreased MPP^+-induced 2,3-DHBA formation in a concentration-

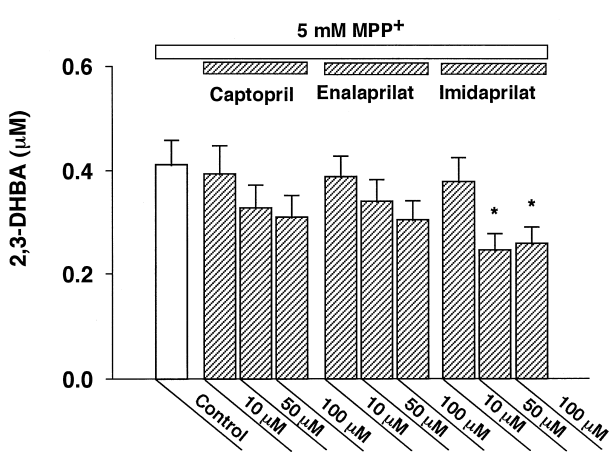

Fig. 3. Inhibitory effect of angiotensin-converting enzyme inhibitors on MPP^+-induced ·OH formation. Angiotensin-converting enzyme inhibitors (diagonally shaded column; captopril, enalapril and imidaprilat) were administered to MPP^+-pre-treated animals and dialysate 2,3-DHBA formation was compared with that of the control (closed column). Values are means ± S.E.M. for six animals. $^*P < 0.05$ vs. control group.

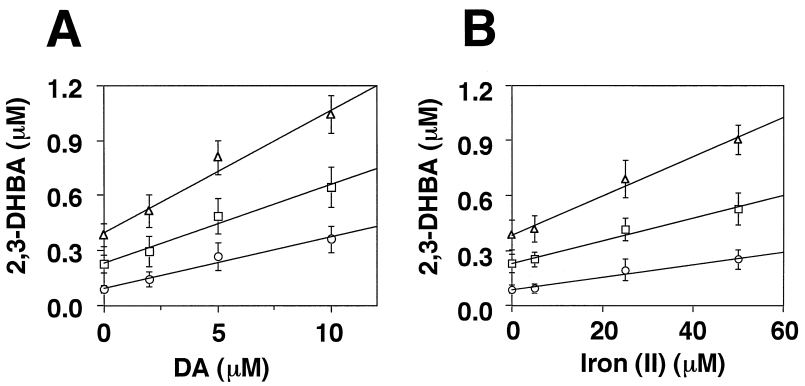

Fig. 4. Effect of imidaprilat on MPP^+-induced ·OH formation. (A) Dose–response relationship between dopamine and the formation of DHBA, the product of the reaction between ·OH and salicylate ·OH. Dopamine and sodium salicylate (0.5 nmol μl^{-1} min^{-1}) were infused through the dialysis probe. Dopamine (0, 2, 5, and 10 μM) was infused to directly through the dialysis probe. (B) Dose–response relationship between iron (II) and the formation of ·OH. Or formation of DHBA, the product of the reaction between ·OH and salicylate. Iron (II) and sodium salicylate (0.5 nmol μl^{-1} min^{-1}) were infused through the dialysis probe. Iron (II) (0, 5, 25, and 50 μM) was administered directly through the dialysis probe. The level of 2,3-DHBA in all three groups (MPP^+-only-treated rats (△) and imidaprilat-treated rats (□) and non-treated rats (○)) was compared. Dialysate samples were assayed immediately by an HPLC-EC procedure. Values are means ± S.E.M. for six animals.

dependent manner over the concentration range of 10–100 μM: the maximum effect, i.e., 39.8 ± 7.9% of control ($n = 6$, $P < 0.05$) was attained at 50 μM imidaprilat. In corresponding experiments with enalaprilat- (50 μM) and captopril- (50 μM) treated animals, the levels of 2,3-DHBA were 20.0 ± 10.6 and 17.0 ± 10.6% of control, respectively. However, these changes were not significant.

To confirm that the dopamine released by MPP^+ evoked ·OH formation, dopamine was administered into the imidaprilat-treated rat striatum through the dialysis probe. When dopamine (0, 2, 5, and 10 μM) was administered to MPP^+-only-treated animals, dopamine increased dose dependently the formation of 2,3-DHBA, showing a positive linear correlation between dopamine and 2,3-DHBA ($R^2 = 0.975$). However, when corresponding experiments were performed with imidaprilat-treated animals, the level of 2,3-DHBA decreased (Fig. 4A). Moreover, to confirm that the ·OH was generated by the Fenton reaction, iron (II) was infused through the dialysis probe. When iron (II) (0, 5, 25, and 50 μM) was administered to MPP^+-pre-treated animals, it produced a dose-dependent increase in the levels 2,3-DHBA, as compared with those in the iron (II)-only-treated group, showing a positive linear correlation ($R^2 = 0.989$) between dopamine and ·OH formation, measured as 2,3-DHBA in the dialysate. However, when corresponding experiments were performed with the imidaprilat-treated animals, the level of 2,3-DHBA decreased (Fig. 4B).

4. Discussion

The present study demonstrated that imidaprilat, a new angiotensin-converting enzyme inhibitor, reduced dopamine-evoked ·OH generation in the extracellular space of the striatum during dopamine release elicited by MPP^+. The present experiment indicates that the pyridinium metabolite of MPTP stimulates the generation of cytotoxic ·OH radicals which can be detected during the sustained dopamine overflow evoked by MPP^+. The drugs were administered by intracranial microdialysis. Oxygen free radicals are very reactive, and the non-enzymatic ·OH adduct of salicylate, 2,3-DHBA, provides an assay to measure ·OH formation both in vitro and in vivo (Floyd et al., 1984; Halliwell et al., 1991). This sensitive salicylate hydroxylation procedure can detect ·OH during Fe^{2+}-catalyzed autoxidation of dopamine in vitro (data not shown). The control level of 2,3-DHBA in brain dialysate was about 10% higher than that in the in vitro perfusion reagent. Accordingly, the concentration profile of the administered compounds in the surrounding interstitial space is unknown. In general, the extracellular concentration of a compound given through a probe never attains the concentration measured in the dialysis probe (Benveniste, 1989). This is an unavoidable limitation of the microdialysis technique that should be kept in mind when interpreting the experimental data.

Dopamine undergoes autoxidation more easily than other catecholamines (Graham, 1984) and enhanced autoxidation of dopamine in the striatum during aging has been documented (Fornstedt et al., 1990). As suggested by data obtained during the investigation of manganese-induced Parkinsonism (Graham, 1984), sustained autoxidation of dopamine could lead to excessive accumulation of toxic quinones and potentially cytotoxic oxygen-free radicals. MPP^+ is one of the most potent dopamine-releasing agents (Obata and Chiueh, 1992). When the level of dopamine in the dialysate increased dramatically following administration of MPP^+ (Fig. 1), the level of 2,3-DHBA was observed to increase in the brain dialysate (Fig. 2). Theoretically, ·OH may be formed in vivo during enzymatic oxidation. The superoxide anion radical (O_2^-) has an ex-

tremely short half-life (Halliwell, 1989) and rapidly undergoes dismutation, yielding H_2O_2. H_2O_2 then undergoes Fenton-type reactions in the presence of iron and yields the highly cytotoxic ·OH (Halliwell, 1989; Ben-Shachar and Youdim, 1991). In addition, ·OH can arise from an interaction between H_2O_2 and O_2^- (Haber–Weiss reaction). A high concentration of imidaprilat prevented the formation of ·OH during infusion of MPP^+ (Fig. 3). Our studies showed that angiotensin-converting enzyme inhibitors prevented MPP^+-induced ·OH formation, measured as 2,3-DHBA, in the rat striatum. The results of our study clearly indicated that the non-SH-containing angiotensin-converting enzyme inhibitor, imidaprilat, is a potent free radical scavenger. The free radical-scavenging action of captopril is believed to be due to the presence of an SH-group in its structure (Bagchi et al., 1989). However, imidaprilat (Yamanaka et al., 1996) and enalaprilat (Suzuki et al., 1993) do not contain an SH-group in their structures. We compared the ability to scavenge ·OH of two non-SH-containing angiotensin-converting enzyme inhibitors (imidaprilat and enalaprilat) with that of an SH-containing angiotensin-converting enzyme inhibitor (captopril). Both SH- and non-SH-containing angiotensin-converting enzyme inhibitors scavenged ·OH and thus, free radical-scavenging action of angiotensin-converting enzyme inhibitors is probably not related only to the presence of the SH group. However, catopril and enalaprilat did not significantly reduce the formation of 2,3-DHBA. It is known that the angiotensin-converting enzyme activity of imidaprilat and enalaprilat is more potent than that of captopril (Kubo et al., 1990, 1991). Therefore, these results seem to indicate that imidaprilat is a more potent antioxidant against MPP^+ neurotoxicity than captopril. Moreover, angiotensin-converting enzyme inhibitors have been shown to potentiate the effect of endogenous bradykinin in animal models and in humans (Seyedi et al., 1977; Prostran et al., 1991). The role of bradykinin in the action of angiotensin-converting enzyme inhibitors has remained controversial, mainly due to the lack of potent and specific bradykinin agents with which to test this hypothesis experimentally. Further research is necessary to confirm the anti-free radical mechanism of bradykinin.

When dopamine was administered to MPP^+-only-treated animals, a marked elevation in the levels of 2,3-DHBA was observed, as compared with those of dopamine-only-treated animals, showing a positive linear correlation ($R^2 = 0.975$) between dopamine and ·OH formation, measured as 2,3-DHBA in the dialysate. However, when corresponding experiments were performed with imidaprilat-treated animals, the levels of 2,3-DHBA were reduced (Fig. 4A). Therefore, the lower ·OH signal cannot be attributed to lower levels of dopamine, because hydroxylation of salicylate did not occur even when dopamine was directly added. This result suggests that the accumulation of endogenous dopamine can lead to the formation of cytotoxic ·OH radicals. Dopamine is known to be autoxidized in the presence of oxygen and transition metals (Graham, 1984; Riederer et al., 1989). The enzyme xanthine oxidase is also thought to be a source of superoxide anion radical (O_2^-). O_2^- itself is somewhat poorly reactive in aqueous solution, but does participate in the reaction in which iron ions are involved, leading to the generation of the more damaging ·OH species. O_2^- has an extremely short half-life and rapidly undergoes dismutation, yielding H_2O_2 which then undergoes a Fenton-type reaction in the presence of iron to yield cytotoxic ·OH (Ben-Shachar and Youdim, 1991). When iron (II) was administered to the MPP^+-pre-treated group, a marked increase in 2,3-DHBA was obtained, as compared with the iron (II)-only-treated group, showing a positive linear correlation ($R^2 = 0.989$) between iron (II) and ·OH formation, measured as 2,3-DHBA in the dialysate. When corresponding experiments were performed with the imidaprilat-treated animals, the levels of 2,3-DHBA were reduced (Fig. 4B). This finding shows that extracellular dopamine is needed for the observed effect of the Fenton-type reaction. It is known that the angiotensin II-induced increase in dopamine release is Ca^{2+}-dependent. However, Sun et al. (1988) demonstrated that intranigral administration of MPP^+ resulted in damage due to an overload of intracellular Ca^{2+}. Therefore, the antioxidant effect of angiotensin-converting enzyme inhibitor may be due to the suppression of the Ca^{2+}-dependent release of dopamine. However, further experiments are necessary to confirm the relation between angiotensin-converting enzyme inhibitor and Ca^{2+}-dependent release of dopamine. The present results indicate that angiotensin-converting enzyme inhibitors may protect against MPP^+-induced ·OH generation in the rat striatum.

Free radical reactions are a part of normal metabolism. The ·OH was generated by the presence of dopamine and oxygen. When produced in excess, radicals can cause tissue injury. These results suggest that non-enzymatic or enzymatic oxidation of dopamine in the extracellular fluid may play a key role in the generation of ·OH free radicals in the brain. ·OH generation is elicited by MPP^+, and ·OH formation parallels the ability of MPP^+ to destroy A9 dopamine neurons when given intranigrally in vivo or in cultures (Sanchez-Ramos et al., 1986; Sun et al., 1988). These data are also consistent with the notion that dopamine autoxidation and sustained dopamine turnover can lead to free radical formation, which in turn causes oxidant damage in the iron-enriched nigral neurons during senescence and in Parkinson's disease (Hirsch et al., 1988; Riederer et al., 1989; Fornstedt et al., 1990; Ben-Shachar and Youdim, 1991). The blockage of dopamine oxidation by imidaprilat may prevent MPP^+-induced ·OH generation. Therefore, the present study indicates that imidaprilat, a new angiotensin-converting enzyme inhibitor, may prevent the formation of ·OH during the oxidation of induced by MPP^+.

These results suggest that the action of angiotensin-converting enzyme inhibitors may involve an anti-free radical

mechanism. Brain microdialysis experiments offer new possibilities for the in vivo study of the therapeutic effect of angiotensin-converting enzymes inhibitors in Parkinson's disease.

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