ELSEVIER

European Journal of Pharmacology 422 (2001) 61–68

ejp

www.elsevier.nl/locate/ejphar

Oxygen inhalation enhances striatal dopamine metabolism and monoamineoxidase enzyme inhibition prevents it: a microdialysis study

Yushi U. Adachi [a,b], Kazuhiko Watanabe [a], Hideyuki Higuchi [c], Tetsuo Satoh [a], E. Sylvester Vizi [b,*]

[a] *Department of Anesthesiology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan*
[b] *Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, PO Box 67, H-1450 Budapest, Hungary*
[c] *Department of Anesthesia, Self Defense Force Central Hospital, 1-2-24 Ikejiri, Setagaya-Ku, Tokyo 154-8522, Japan*

Received 18 December 2000; received in revised form 16 May 2001; accepted 18 May 2001

Abstract

In order to explore the effect of normobaric oxygen on the extracellular level of dopamine and its metabolites, oxygen (30, 60 and 90%) was administered to freely moving rats after the animals had been pretreated with either monoamineoxidase (MAO)-A and -B inhibitors (0.1 or 1 mg kg^{-1} of clorgyline, 1 or 10 mg kg^{-1} of selegiline and 75 mg kg^{-1} pargyline) or control solution. The levels of dopamine and its metabolites were monitored in microdialysis samples collected every 20 min and directly applied to an on-line high-performance liquid chromatograph combined with electrochemical detection. Normobaric oxygen inhalation decreased the level of extracellular dopamine and increased that of 3,4-dihydroxyphenylacetic acid (DOPAC) in a concentration-dependent manner. These changes were partly prevented by pre-treatment with low doses of selegiline or clorgyline, i.e. by conditions in which monoamineoxidase-A or -B was inhibited. When both isoforms of monoamineoxidase were inhibited, there was a drastic increase in extracellular concentrations of dopamine and 3-methoxytyramine, and the levels of DOPAC and homovanilic acid (HVA) were very low. These results indicate that the intracellular metabolism of cytoplasmic dopamine is enhanced by normobaric hyperoxia in rat striatum.

Keywords: Normobaric oxygen; Dopamine; Striatum; Monoamineoxidase inhibition; (Rat)

1. Introduction

Various investigators (Huggins and Nelson, 1975; Singh and Banister, 1981, 1983; Mialon et al., 1990) have studied the central nervous system toxicity of hyperbaric oxygenation, called the *Paul Bert* effect. However, there exists minimal information on the effect of normobaric oxygenation on the nervous system (Bickford et al., 1999). While aerobes need oxygen for survival, oxygen in concentrations greater than those found in normal air (20.9%) have long been known to be toxic (Balentine and Dean, 1982). Therefore, we studied the effect of normobaric inhalation of oxygen administered at different concentrations (30%, 60% and 90%) on the striatal level of extracellular dopamine, using microdialysis techniques in awake freely moving rats. In order to explore the mode of action of oxygen inhalation on dopamine metabolism, monoamineoxidase inhibitors, including clorgyline, selective for monoamineoxidase-A (Johnston, 1968; Murphy et al., 1998), selegiline, selective for monoamineoxidase-B (Knoll et al., 1978; Harsing et al., 1979), and pargyline, a non-selective monoamineoxidase inhibitor (Cumming et al., 1992; Tuomainen et al., 1996), were administered with or without a high level of oxygen inhalation. Evidence was obtained that the release of dopamine is reduced, but the level of 3,4-dihydroxyphenylacetic acid (DOPAC) in the dialysate is increased, indicating that the intraneuronal metabolism of cytoplasmic dopamine is increased by normobaric hyperoxia.

2. Materials and methods

2.1. Microdialysis study

Adult male Sprague–Dawley rats, weighing 280–320 g, were used (CLEA Japan, Tokyo, Japan) throughout the

* Corresponding author. Tel.: +36-1-210-9421; fax: +36-1-210-9423.
E-mail address: esvizi@koki.hu (E.S. Vizi).

0014-2999/01/$ - see front matter
PII: S0014-2999(01)01074-3

experiments. The animals were housed in an animal room controlled at 20–22 °C and illuminated with a 12-h light–dark cycle (lighted from 07:00 to 19:00). The animals were allowed food and drinking water ad libitum. The experiments were approved by the Committee for Animal Research and Welfare of our college.

Rats were anesthetized with sevoflurane and ventilated through an oro-tracheal tube, as described earlier (Adachi et al., 1999, 2000a,b). Surgical operations were performed under the additional topical application of 1% lidocaine. Using a stereotaxic frame, a unilateral guide cannula was implanted just above the striatum (AP +0.6 mm, ML +3.0 mm, DV −3.8 mm) according to the atlas of Paxinos and Watson (1998). The rats were allowed to recover for at least 2 days before experiments were started. After the experiment, rats were killed by inhalation of excess isoflurane and intravenous injection of thiopental. The placement of a microdialysis probe was verified by histological examination.

Microdialysis probes were purchased from EICOM (Kyoto Japan) (o.d. 0.22 mm, membrane length 3 mm, polycarbonate tubing, cut-off mol. wt. 50,000). On the day of the experiment, at about 7:00 a.m., the rat was briefly anesthetized with sevoflurane. The probe was inserted carefully into the striatum through a guide cannula and fixed to the cannula with a screw. This procedure was performed within 5 min of anesthetization, and the rat was immediately placed in a clear open Plexiglas box (15 l in capacity, 27 cm in diameter and 26 cm in height) for recovery. After recovery, the probe was constantly perfused with Ringer's solution (Osborne et al., 1990; Stahle et al., 1990; Miyano et al., 1993; Fink-Jensen et al., 1994; Adachi et al., 2000a) (in mEq l^{-1}: 147.0 Na^+, 4.0 K^+, 2.4 Ca^{2+}, 155.8 Cl^-) at a flow rate of 2 μl min^{-1} using a micro-infusion pump (ESP-64, EICOM, Kyoto, Japan), and the baseline levels of dopamine and its metabolites were determined. Samples were collected every 20 min and directly injected into an online analytical system with an auto-injector (EAS-20, EICOM). The contents of dopamine, DOPAC, 3-methoxytyramine, and homovanillic acid (HVA) in each dialysate (40 μl/20 min) were determined by high-pressure liquid chromatography with an electrochemical detector (ECD-300, EICOM) as described earlier (Milusheva et al., 1996; Adachi et al., 2000a). The detection limit for each of the compounds was about 1.0 pg per sample.

Dopamine and its metabolites reached stable baseline levels in about 4.5 h after the implantation of a microdialysis probe. Thus, at least six dialysate samples, each containing 40 μl of dialysate and collected every 20 min, were obtained before a pharmacological experiment was started. The mean value obtained from the last three samples was used as the baseline level, and the amount of dopamine or its metabolites in that baseline sample was taken as 100%. The fraction at which the O_2 inhalation started will be termed hereafter fraction number 1 (Fr. 1). Any pharmacological manipulation is indicated on the figures. Four dialysate samples were obtained before pretreatment with drugs.

Each rat was put in the semi-closed Plexiglas box, into which 100% air was initially introduced at a rate of 5 l min^{-1} for about 5 min until a steady state was achieved, then 30%, 60% or 90% oxygen was applied at a rate of 3 l min^{-1} for 1 h from Fr 1. In the control group, air was administered at a rate of 3 l min^{-1} for the same time period. The oxygen or air was introduced to the center of the box and escaped through several small holes for connecting the rat to analytical apparatuses. The dialysates were collected for 4 h after the 1-h inhalation was stopped. During each experiment, the concentration of oxygen in the box was monitored using an infrared anesthetic gas analyzer (Capnomac Ultima, Datex Helsinki Finland). Immediately after the 1-h inhalation of oxygen, the gas in the box was exchanged for room air by forced ventilation.

In another series of experiments, rats were pre-treated with clorgyline, selegiline, or pargyline, drugs affecting monoamineoxidase and dopaminergic activity. While clorgyline is a monoamineoxidase-A (Johnston, 1968; Murphy et al., 1998) and selegiline is a monoamineoxidase-B selective inhibitor (Knoll et al., 1978; Harsing et al., 1979), pargyline is a non-selective monoamineoxidase inhibitor (Cumming et al., 1992; Tuomainen et al., 1996). Clorgyline at a dose of 0.1 or 1 mg kg^{-1} (0.6 ml/300 g), selegiline 1 or 10 mg kg^{-1} (0.6 ml/300 g), or pargyline 75 mg kg^{-1} (0.6 ml/300 g) was intraperitoneally injected. Eighty minutes after treatment with monoamineoxidase inhibitors, the animals were exposed to 30% or 90% of oxygen for 1 h.

2.2. Materials

Each drug was purchased from ICN (ICN Biomedicals, Aurora, OH, USA). Clorgyline, selegiline, and pargyline were dissolved in physiological saline to 0.05 or 0.5 mg ml^{-1}, 0.5 or 5 mg ml^{-1} and 37.5 mg ml^{-1}, respectively.

2.3. Statistical analysis

Data were analyzed by two-way analysis of variance with drugs as a between-subjects variable and time as a within-subject variable. Significant ($P < 0.05$) drug–time interactions were followed for each drug by one-way analysis of variance and by subsequent Newman–Keuls post-hoc comparison (NCSS 2000, Kaysville, UT, USA).

3. Results

In the untreated control group, the rats inhaled air, i.e. 20.9% oxygen. The dialysates of these animals maintained a constant level of dopamine throughout the experiment (Fig. 1). In contrast, the levels of dopamine metabolites in the samples decreased significantly with time. At the end

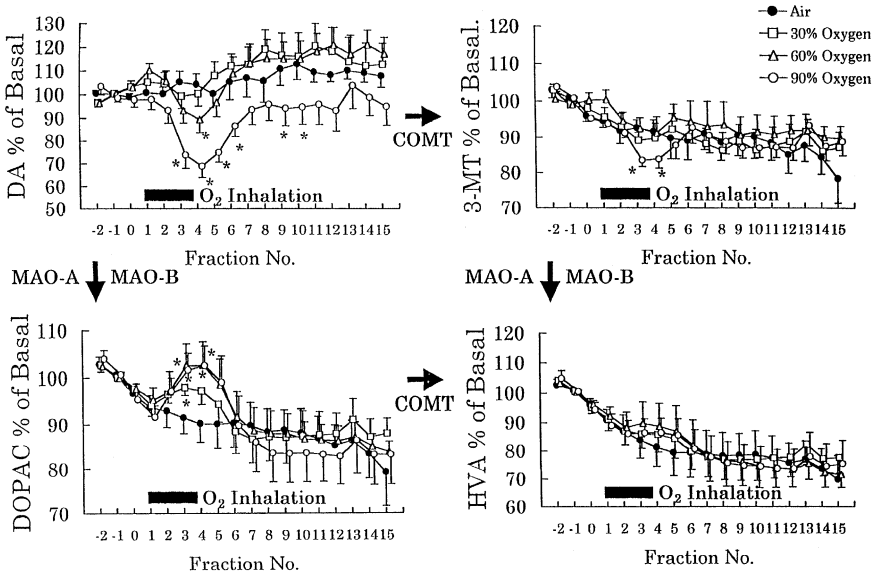

Fig. 1. Effect of oxygen inhalation on the levels of extracellular dopamine (DA) and its metabolites (3-methoxytyramine, DOPAC and HVA). In this and the following figures, the ordinate of each graph shows the level of dopamine or its metabolites expressed as the percentage of the baseline level, which was the mean of three consecutive values observed immediately before the start of the pharmacological manipulations; each point is the mean ± SEM ($n = 6$); dialysate fractions were obtained every 20 min, and asterisks indicate significant changes ($^{*}P < 0.05$; Newman–Keuls post-hoc comparison test) compared to the control group value at the corresponding time point. Monoamineoxidase-A and monoamineoxidase-B enzymes are responsible for the metabolism of dopamine and 3-methoxytyramine and the production of 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Oxygen (O_2) inhalation at concentrations of 30%, 60% and 90% is indicated. Note that catechol-*o*-methyltransferase (COMT) is the enzyme that produces 3-methoxytyramine from dopamine and HVA from DOPAC.

of the experiment, the levels of 3-methoxytyramine, DOPAC and HVA were reduced to 78.4 ± 7.0, 79.2 ± 7.6, and 69.9 ± 8.5%, respectively. In the present study, the above changes in dopamine and its metabolites in the dialysate were taken as baseline, and drug-induced changes were statistically compared with this baseline.

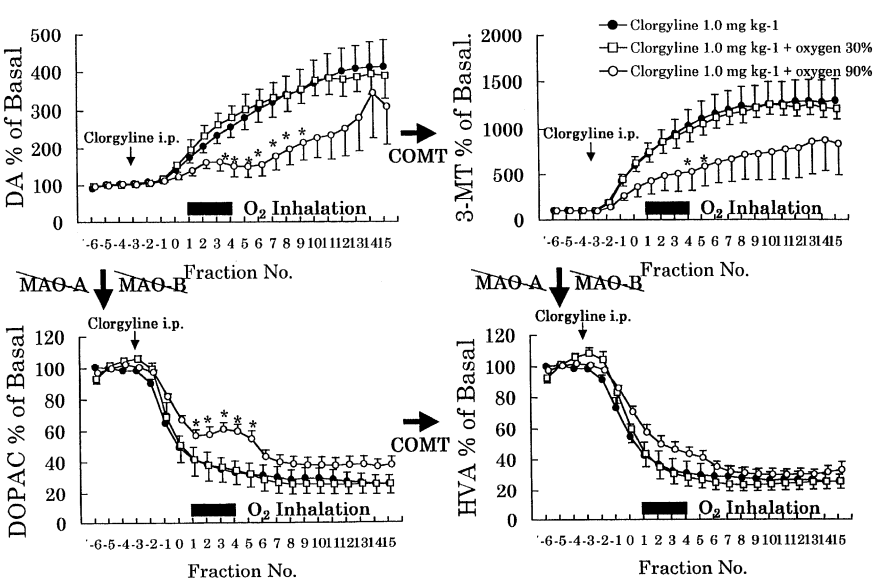

Fig. 2. Effects of oxygen inhalation on the levels of extracellular dopamine and its metabolites (DOPAC, 3-methoxytyramine and HVA) in rats pretreated with clorgyline 1 mg kg^{-1} intraperitoneally. Under this condition, the activities of both monoamineoxidase-A and monoamineoxidase-B enzymes were reduced. $n = 6$ in each group. For further explanations, see the legend of Fig. 1. Note that clorgyline at this dose, at which both monoaminoxidase enzymes were inhibited, increased the extraneuronal concentration of dopamine and reduced that of DOPAC and HVA. Note that the effect of oxygen inhalation at a concentration of 90% on dopamine, DOPAC and 3-methoxytyramine levels was reduced by clorgyline.

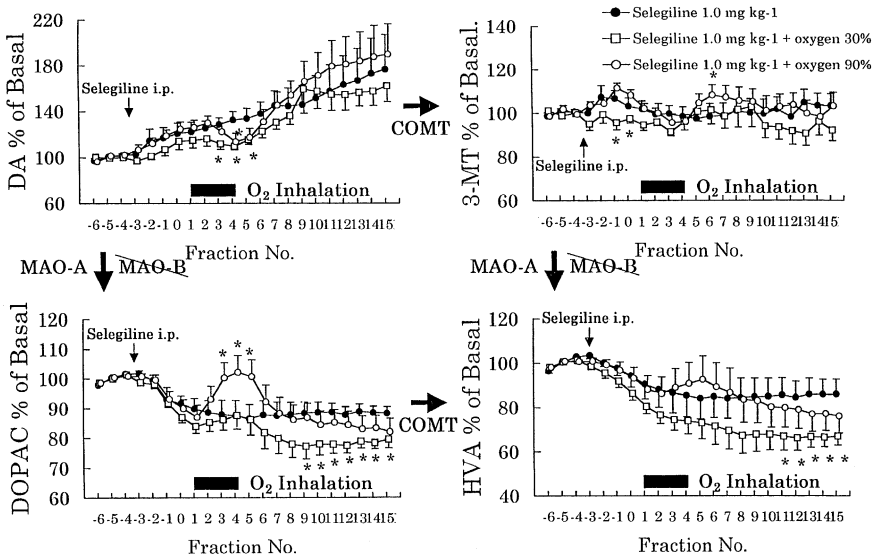

Fig. 3. Effects of oxygen inhalation on the levels of extracellular dopamine and its metabolites (DOPAC, 3-methoxytyramine and HVA) in rats pretreated with selegiline 1 mg kg^{-1} intraperitoneally. Under this condition, the activities of monoamineoxidase-B was inhibited. $n = 6$ in each group. For further explanations, see the legend of Fig. 1. Note that selegiline partly antagonized the effect of O_2 inhalation on dopamine and DOPAC levels.

3.1. Effects of normobaric hyperoxia

When oxygen in different concentrations was inhaled, there were significant changes in the levels of dopamine and its metabolites in the extracellular space of the striatum.

As shown in Fig. 1, even during the inhalation of oxygen at concentrations of 60% and 90%, the levels of dopamine in the samples were significantly decreased and the levels of DOPAC were increased. DOPAC levels were enhanced even at an O_2 concentration of 30% (Fig. 1). The effect of oxygen was concentration dependent. During a 4-h recovery period from oxygen inhalation, the levels of dopamine and metabolites recovered without a delay for the group that inhaled 60% oxygen, whereas in the 90% oxygen group the dopamine reduction was prolonged.

3.2. Effects of clorgyline, selegiline, or pargyline on oxygen-induced changes in dopamine and metabolites levels

Initially, the animals inhaled air. After four samples were collected, monoamineoxidase inhibitors were intraperitoneally injected. Monoamineoxidase inhibitors markedly influenced the extracellular levels of dopamine, DOPAC, 3-methoxytyramine and HVA in striatal dialysates

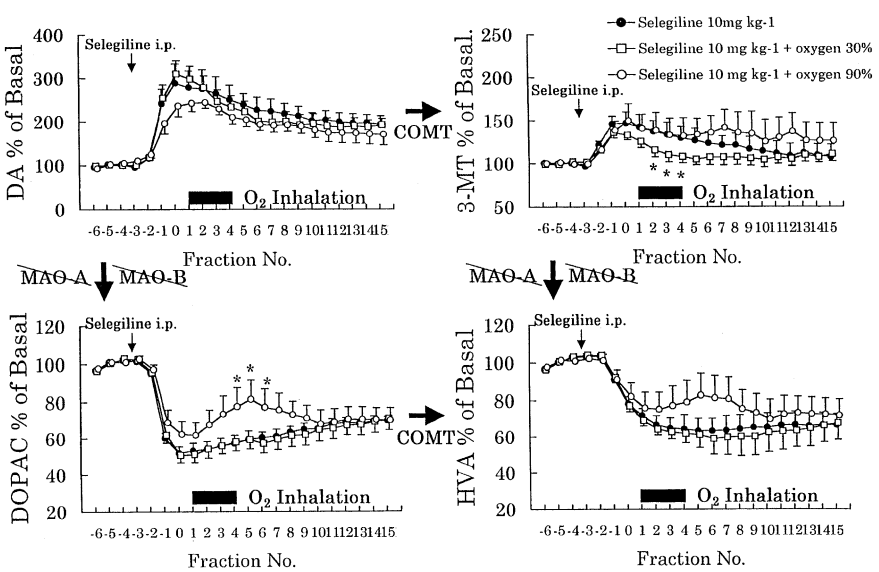

Fig. 4. Effects of oxygen (O_2) inhalation on the levels of extracellular dopamine and its metabolites (DOPAC, 3-methoxytyramine and HVA) in rats pretreated with selegiline 10 mg kg^{-1} intraperitoneally. Under this condition, the activities of monoamineoxidase-A and monoamineoxidase-B enzymes were inhibited. $n = 6$ in each group. For further explanations, see the legend of Fig. 1 and the text.

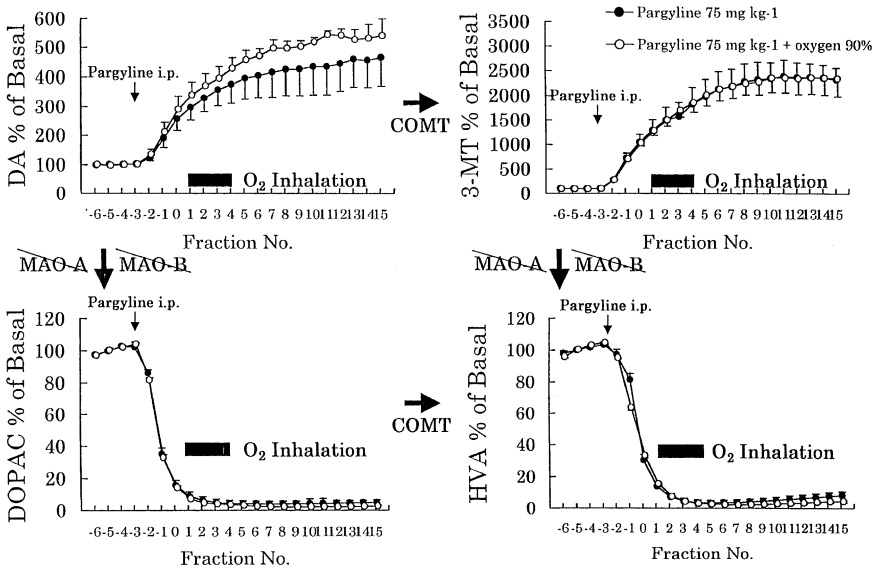

Fig. 5. Effects of oxygen (O_2) inhalation on the levels of extracellular dopamine and its metabolites (DOPAC, 3-methoxytyramine and HVA) in rats pretreated with pargyline (75 mg kg^{-1} intraperitoneally). $n = 4$ in each group. For further explanations, see the legend of Fig. 1. Note that under conditions in which both monoamineoxidase-A and monoamineoxidase-B enzymes were inhibited, O_2 inhalation (90%) had no effect.

(Figs. 2–5). Clorgyline, injected at the dose of 0.1 mg kg^{-1} under conditions when only the monoamineoxidase-A enzyme was inhibited, increased the quantity of dopamine in the samples (140.2 ± 4.6%, $P < 0.05$). It did not reduce the extracellular levels of DOPAC and HVA (data not shown), and did not antagonize the effect of oxygen inhalation at 30% and 90% (data not shown). After the injection of 1 mg kg^{-1} clorgyline (Fig. 2), the levels of dopamine and 3-methoxytyramine were increased. Under this condition, both DOPAC and HVA levels were drastically reduced (Fig. 2) and the effect of oxygen inhalation at 90% was partly antagonized. Selegiline, at doses of 1 and 10 mg kg^{-1}, enhanced dopamine levels and reduced the ability of oxygen inhalation to decrease dopamine levels (Figs. 3 and 4). Selegiline at 10 mg kg^{-1} drastically increased the extracellular levels of dopamine and 3-methoxytyramine, and reduced those of DOPAC and HVA, i.e. under conditions when both monoamineoxidase-A and monoamineoxidase-B enzymes were inhibited (cf. Butcher et al., 1990). In these animals, inhalation of 90% oxygen increased DOPAC levels (Fig. 4), while in control experiments (Fig. 1) inhalation of 30% oxygen was effective to the same extent. Pre-treatment with pargyline completely abolished the ability of oxygen inhalation to reduce the extracellular concentration of dopamine (Fig. 5). Pargyline increased dopamine and 3-methoxytyramine levels and completely blocked DOPAC and HVA from being produced from dopamine and 3-methoxytyramine, respectively.

4. Discussion

Normobaric oxygen inhalation reduced the extracellular level of dopamine and increased that of DOPAC in a concentration-dependent manner. Since dopamine is the major substrate of the monoamineoxidase-A enzyme in the rat striatum (Butcher et al., 1990; Finberg et al., 1995), and DOPAC is the major metabolite of freshly synthesized cytoplasmic dopamine (Zetterström et al., 1988) ready to be taken up by vesicles and released, it seems likely that normobaric hyperoxia increases the metabolism of dopamine in the cytoplasm.

The effect of 90% oxygen in reducing dopamine levels in the extracellular space was partly prevented by 1 mg kg^{-1} clorgyline (Fig. 2), i.e. under conditions in which both isoforms of monoaminoxidase were inhibited. 10 mg kg^{-1} selegiline and 75 mg kg^{-1} pargyline pretreatment completely prevented oxygen inhalation from reducing extracellular dopamine levels and increasing the appearance of its main metabolite, DOPAC, in the striatal extracellular space (Figs. 3–5). The relatively selective inhibition of monoamineoxidase-A with clorgyline (0.1 mg kg^{-1}) and monoamineoxidase-B (Fig. 3) with a low dose of selegiline (1 mg kg^{-1}) was not very effective in preventing oxygen inhalation from reducing dopamine and increasing DOPAC levels in the extracellular space. However, under conditions when both monoamineoxidase-A and monoamineoxidase-B enzymes were completely inhibited (Waldmeier and Felner, 1978; Heikkila et al., 1990; Butcher et al., 1990), dopamine and 3-methoxytyramine levels were high and DOPAC and HVA levels were either not detectable (Fig. 5) or very low (Figs. 2 and 4). Clorgyline-treated rats were more sensitive to oxygen inhalation, whereas selegiline-treated rats were less sensitive. These results suggest that during oxygen inhalation, monoamineoxidase-B is more important for dopamine metabolism. These results are in good agreement with those showing that in clorgyline-treated rats dopamine

metabolism is fully dependent of the actual activity of monoamineoxidase-B (Harsing and Vizi, 1984; Butcher et al., 1990).

At a high dose of selegiline, the possibility that the release of dopamine and the changes in metabolite levels may be due to an amphetamine-like effect of the compound should be taken into account. Indeed, amphetamine was shown (Butcher et al., 1988) to release dopamine and to increase 3-methoxytyramine and to decrease DOPAC and HVA levels in the striatum. Therefore, the possibility that the effect of selegiline on the levels of dopamine and its metabolites may be, at least, partly due to its amphetamine-like activity cannot be excluded. Nevertheless, the fact that the effect of selegiline was similar to that of pargyline, a compound without an amphetamine-like effect and a strong monoamineoxidase-A and monoamineoxidase-B inhibitor (Cumming et al., 1992; Tuomainen et al., 1996), indicated that the inhibition of dopamine metabolism by monoaminoxidase enzyme is certainly involved in the effect of selegiline.

Dopamine is a substrate for both isoforms of monoamineoxidase in the striatum (Juorio et al., 1994; Tuomainen et al., 1996). Although it has been suggested that the transporter, expressed extrasynaptically (Kuhar, 1998), limits the extracellular lifetime of dopamine in the striatum (Budygin et al., 1999; Peters and Michael, 2000), it has been shown (Mercuri et al., 1997) that the termination of dopamine action in the central nervous system is also controlled by monoamineoxidase-A and -B enzymes. This conclusion is supported by our experiments in which the inhibition of both monoamineoxidase-A and monoamineoxidase-B enzymes by pargyline resulted in a long-lasting and sustained high extracellular level of dopamine (Fig. 5). The overwhelming majority of dopaminergic varicosities do not make synaptic contact (Van Horne et al., 1992; Schneider et al., 1994) and dopamine released from these nonsynaptic dopaminergic varicosities diffuses far away (Vizi, 1984a,b, 2000; Kiss and Vizi, 2001) and controls neuronal activity.

The finding that DOPAC synthesis was completely blocked (98%) by the dose of pargyline that was able to inhibit both isoforms of monoamineoxidase (Cumming et al., 1992; Tuomainen et al., 1996) and the fact that exogenously administered dopamine is also converted into DOPAC (Zetterström et al., 1988) indicate that in the rat both isoforms are involved in the metabolism of dopamine. Monoamineoxidase-B may be responsible for the destruction of freshly synthesized dopamine in the cytoplasm and in the pool of dopamine readily available for release, while monoamineoxidase-A may affect the metabolism of dopamine already released into the extracellular space. Previous investigators have reported that dopamine metabolism is mediated principally by monoamineoxidase-A in the rat striatum (Butcher et al., 1990; Finberg et al., 1995). However, dopamine is a more preferred substrate for monoamineoxidase-B than for monoamineoxidase-A. Selegiline has been applied to patients with Parkinson's disease and has been reported to be beneficial (Jenner and Olanow, 1996; Gerlach et al., 1996), but this was questioned by some investigators (Ben-Shlomo et al., 1998). It is noteworthy that oxidative stress might primarily modify the activity of monoamineoxidase-B, rather than that of monoamineoxidase-A, which principally regulates dopamine metabolism. Monoamineoxidase-B might be more sensitive to oxidative stress and may produce more free radicals.

Recently, the relationship between oxidative stress and the pathogenesis of Parkinson's disease has been discussed (Jenner and Olanow, 1996; Berman and Hastings, 1999; Cohen, 2000). Oxidative stress in Parkinson's disease may also arise, in part from the metabolism of dopamine itself through both chemical and enzymatic pathways (Jenner and Olanow, 1996). Dopamine released via exocytosis or reversal of the dopamine transporter (Abarca and Bustos, 1999; Kiss et al., 1999; Olivier et al., 1999) may produce hydroxyl radicals (OH^-) and may also be cytotoxic (McLaughlin et al., 1998; Noh et al., 1999; Jacobsson and Fowler, 1999). The autoxidation of dopamine leads to the production of semiquinones, which are themselves toxic and which may also lead to the generation of reactive oxygen species (Halliwell and Gutteridge, 1985a; Olanow, 1990; Jacobsson and Fowler, 1999). The enzymatic metabolism of dopamine leads not only to the production of the deaminated metabolites DOPAC and HVA, but also to the generation of H_2O_2 (Halliwell and Gutteridge, 1985b; Olanow, 1990). H_2O_2 would normally be inactivated by glutathione in a reaction catalyzed by glutathione peroxidase (Weber et al., 1990). However, if this reducing glutathione system were impaired or deficient, H_2O_2 might be converted by the iron-mediated *Fenton* reaction into the highly reactive OH^-. This hydroxyl product may cause cell death (Mohanakumar et al., 1994; Haavik et al., 1997).

The results of the present investigation demonstrate that extracellular dopamine levels are reduced by oxygen inhalation. If the oxidative stress derived from oxygen inhalation caused damage or death to neurons, the extracellular dopamine level would have been increased (Globus et al., 1988; Koorn et al., 1993; Milusheva et al., 1992, 1996). However, this was not the case with normobaric oxygen inhalation. Therefore, it seems likely that the lethality of oxidative stress might require more oxygenation than normal, including hyperbaric administration (Huggins and Nelson, 1975; Singh and Banister, 1981, 1983; Mialon et al., 1990) or an intrinsic disorder, for example, Parkinson's disease (Jenner and Olanow, 1996; Berman and Hastings, 1999; Cohen, 2000).

In conclusion, the present study clearly shows that normobaric oxygen inhalation decreases the levels of extracellular dopamine and increases those of DOPAC, indicating that the metabolism of cytoplasmic dopamine is enhanced by normobaric hyperoxia in the rat striatum. Since considerable difference was shown (Ivanov et al.,

1999) between brain tissue oxygen tensions under normoxia versus normobaric hyperoxia, at a distance of 10–50 μm from the arteriole walls, it can be concluded that oxygen inhaled by animals diffuses far away from the microvessels and is able to influence chemical transmission in the striatum. The advantage of selegiline treatment is that it selectively inhibits the cytoplasmic destruction of dopamine by mitochondrial monoamineoxidase-B, thereby preventing oxidative stress from increasing metabolism, depleting dopaminergic terminals, and producing free radicals (e.g. OH^-, $\cdot OH$), the endogenous compounds responsible for neuronal injury (Halliwell and Gutteridge, 1984, 1985a). When both isoforms of monoamineoxidase were inhibited, there was a drastic increase in extracellular concentrations of dopamine and 3-methoxytyramine and very low levels of DOPAC and HVA. These findings indicate that the monoamineoxidase-A and monoamineoxidase-B enzymes are involved in the metabolism of dopamine in the striatum. Furthermore, our findings suggest that even normobaric oxygen inhalation accelerates the metabolism of cytoplasmic dopamine in the striatum.

Acknowledgements

We express our sincere thanks to Dr. Kohichi Okamoto, Prof. Junko Okamoto and Ms. Laura Franklin for their reviewing and commenting on the manuscript of this paper.

References

Abarca, J., Bustos, G., 1999. Differential regulation of glutamate, aspartate and gamma-amino-butyrate by *N*-methyl-D-aspartate receptors in rat striatum after partial and extensive lesions to the nigro-striatal dopamine pathway. Neurochem. Int. 35, 19–33.

Adachi, Y., Uchihashi, Y., Watanabe, K., Satoh, T., 1999. The effect of sevoflurane and isoflurane on striatal dopamine of awake freely moving rats using in vivo microdialysis study. Masui (Jpn. J. Anesth.) 48, 960–965.

Adachi, Y., Uchihashi, Y., Watanabe, K., Satoh, T., 2000a. Halothane anesthesia decreases the extracellular level of dopamine in rat striatum: a microdialysis study in vivo. J. Anesth. 14, 82–90.

Adachi, Y., Uchihashi, Y., Watanabe, K., Satoh, T., 2000b. Halothane anesthesia decreases the level of interstitial striatal dopamine of awake freely moving rats in an in vivo microdialysis study. Masui (Jpn. J. Anesth.) 49, 139–144.

Balentine, J.D., Dean Jr., D.L., 1982. Calcium-induced spongiform and necrotizing myelopathy. Lab. Invest. 47, 286–295.

Ben-Shlomo, Y., Churchyard, A., Head, J., Hurwitz, B., Overstall, P., Ockelford, J., Lees, A.J., 1998. Investigation by Parkinson's disease research group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomised trial and confidential inquiry. Br. Med. J. 316, 1191–1196.

Berman, S.B., Hastings, T.G., 1999. Dopamine oxidation alters mitochondrial respiration and induces permeability transition in brain mitochondria: implications for Parkinson's disease. J. Neurochem. 73, 1127–1137.

Bickford, P.C., Chadman, K., Williams, B., Shukitt-Hale, B., Holmes, D., Taglialatela, G., Joseph, J., 1999. Effect of normobaric hyperoxia on two indexes of synaptic function in Fisher 344 rats. Free Radical Biol. Med. 26, 817–824.

Budygin, E.A., Gainetdinov, R.R., Kilpatrick, M.R., Rayevsky, K.S., Mannisto, P.T., Wightman, R.M., 1999. Effect of tolcapone, a catechol-*O*-methyltransferase inhibitor, on striatal dopaminergic transmission during blockade of dopamine uptake. Eur. J. Pharmacol. 370, 125–131.

Butcher, S.P., Fairbrother, I.S., Kelly, J.S., Arbuthnott, G.W., 1988. Amphetamine-induced dopamine release in the rat striatum: an in vivo microdialysis study. J. Neurochem. 50, 346–355.

Butcher, S.P., Fairbrother, I.S., Kelly, J.S., Arbuthnott, G.W., 1990. Effects of selective monoamine oxidase inhibitors on the in vivo release and metabolism of dopamine in the rat striatum. J. Neurochem. 55, 981–988.

Cohen, G., 2000. Oxidative stress, mitochondrial respiration, and Parkinson's disease. Ann. N.Y. Acad. Sci. 899, 112–120.

Cumming, P., Brown, E., Damsma, G., Fibiger, H., 1992. Formation and clearance of interstitial metabolites of dopamine and serotonin in the rat striatum: an in vivo microdialysis study. J. Neurochem. 59, 1905–1914.

Finberg, J.P.M., Goldstein, W.D.S., Kopin, I.J., Bankiewicz, K.S., 1995. Influence of selective inhibition of monoamine oxidase A or B on striatal metabolism of L-DOPA in hemiparkinsonian rats. J. Neurochem. 65, 1213–1220.

Fink-Jensen, A., Ingwersen, S.H., Nielsen, P.G., 1994. Halothane anesthesia enhances the effect of dopamine uptake inhibition on interstitial levels of striatal dopamine. Naunyn-Schmiedeberg's Arch. Pharmacol. 350, 239–244.

Gerlach, M., Youdim, M.B.H., Riederer, P., 1996. Pharmacology of selegiline. Neurology 47 (Suppl. 3), S137–S145.

Globus, M.Y., Busto, R., Dietrich, W.D., Martinez, E., Valdes, I., Ginsberg, M.D., 1988. Effect of ischemia on the in vivo release of striatal dopamine, glutamate, and gamma-aminobutyric acid studied by intracerebral microdialysis. J. Neurochem. 51, 1455–1464.

Haavik, J., Almas, B., Flatmark, T., 1997. Generation of reactive oxygen species by tyrosine hydroxylase: a possible contribution to the degeneration of dopaminergic neurons? J. Neurochem. 68, 328–332.

Halliwell, B., Gutteridge, J.M., 1984. Lipid peroxidation, oxygen radicals, cell damage, and antioxidant therapy. Lancet 8391, 1396–1397.

Halliwell, B., Gutteridge, J., 1985a. Oxygen radicals and the nervous system. Trends Neurosci. 8, 22–29.

Halliwell, B., Gutteridge, J.M., 1985b. The importance of free radicals and catalytic metal ions in human diseases. Mol. Aspects Med. 8, 89–193.

Harsing, L.G., Vizi, E.S., 1984. Release of endogenous dopamine from rat isolated striatum: effect of clorgyline and (−)-deprenyl. Br. J. Pharmac. 83, 741–749.

Harsing Jr., L.G., Magyar, K., Tekes, K., Vizi, E.S., Knoll, J., 1979. Inhibition by deprenyl of dopamine uptake in rat striatum: a possible correlation between dopamine uptake and acetylcholine release inhibition. Pol. J. Pharmacol. Pharm. 31, 297–307.

Heikkila, R.E., Terleckyj, I., Sieber, B.A., 1990. Monoamine oxidase and the bioactivation of MPTP and related neurotoxines: relevance to DATATOP. J. Neural. Transm. 32, 217–227, Suppl.

Huggins, A.K., Nelson, D.R., 1975. The effect of hyperbaric oxygenation on the levels of 5-hydroxytryptamine, noradrenaline, dopamine and free aminoacids in whole mouse brain. J. Neurochem. 25, 117–121.

Ivanov, K.P., Sokolova, I.B., Vovenko, E.P., 1999. Oxygen transport in the rat brain cortex at normobaric hyperoxia. Eur. J. Appl. Physiol. Occup. Physiol. 80, 582–587.

Jacobsson, S.O., Fowler, C.J., 1999. Dopamine and glutamate neurotoxicity in cultured chick telencephali cells: effects of NMDA antagonists, antioxidants and MAO inhibitors. Neurochem. Int. 34, 49–62.

Jenner, P., Olanow, W.C., 1996. Oxidative stress and the pathogenesis of Parkinson's disease. Neurology 47 (Suppl. 3), S161–S170.

Johnston, J.P., 1968. Some observations upon a new inhibitor of monoamine oxidase in brain tissue. Biochem. Pharmacol. 17, 1285–1297.

Juorio, A.V., Paterson, I.A., Zhu, M.Y., 1994. Dopamine metabolism in the guinea pig striatum: role of monoamine oxidase A and B. Eur. J. Pharmacol. 254, 213–220.

Kiss, J.P., Vizi, E.S., 2001. Nitric oxide: a link between synaptic and nonsynaptic transmission. Trends Neurosci. 24, 211–215.

Kiss, J.P., Hennings, E.C., Zsilla, G., Vizi, E.S., 1999. A possible role of nitric oxide in the regulation of dopamine transporter function in the striatum. Neurochem. Int. 34, 345–350.

Knoll, J., Ecsery, Z., Magyar, K., Satory, E., 1978. Novel (−)deprenyl-derived selective inhibitors of B-type monoamine oxidase. The relation of structure to their action. Biochem. Pharmacol. 27, 1739–1747.

Koorn, R., Kahn, R., Brannan, T.S., Martinez-Tica, J., Weinberger, J., Reich, D.L., 1993. Effect of isoflurane and halothane on in vivo ischemia-induced dopamine release in the corpus striatum of the rat. Anesthesiology 79, 827–835.

Kuhar, M.J., 1998. Recent biochemical studies of the dopamine transporter—a CNS drug target. Life Sci. 62, 1573–1575.

McLaughlin, B.A., Nelson, D., Erecinska, M., Chesselet, M.F., 1998. Toxicity of dopamine to striatal neurons in vitro and potentiation of cell death by a mitochondrial inhibitor. J. Neurochem. 70, 2406–2415.

Mercuri, N.B., Scarponi, M., Bonci, A., Siniscalchi, A., Bernardi, G., 1997. Monoamine oxidase inhibition causes a long-term prolongation of the dopamine-induced responses in rat midbrain dopaminergic cells. J. Neurosci. 17, 2267–2272.

Mialon, P., Caroff, J., Barthelemy, L., Bigot, J.C., 1990. Ammonia and monoamine concentrations in two brain areas in rats after one hyperoxic seizure. Aviat., Space Environ. Med. 61, 28–32.

Milusheva, E.A., Doda, M., Pasztor, E., Lajtha, A., Sershen, H., Vizi, E.S., 1992. Regulatory interactions among axon terminals affecting the release of different transmitters from rat striatal slices under hypoxic and hypoglycemic conditions. J. Neurochem. 59, 946–952.

Milusheva, E.A., Doda, M., Baranyi, M., Vizi, E.S., 1996. Effect of hypoxia and glucose deprivation on ATP level, adenylate energy change and $(Ca^{2+})_o$-dependent and independent release of (^{3}H)dopamine in rat striatal slices. Neurochem. Int. 28, 501–507.

Miyano, K., Tanifuji, Y., Eger, E.I., 1993. II. The effect of halothane dose on striatal dopamine: an in vivo microdialysis study. Brain Res. 605, 342–344.

Mohanakumar, K.P., deBartolomeis, A., Wu, R.M., Yeh, K.J., Sternberger, L.M., Peng, S.Y., Murphy, D.L., Chiueh, C.C., 1994. Ferrous–citrate complex and nigral degeneration: evidence for free-radical formation and lipid peroxidation. Ann. N.Y. Acad. Sci. 738, 392–399.

Murphy, D.L., Karoum, F., Pickar, D., Cohen, R.M., Lipper, S., Mellow, A.M., Tariot, P.N., Sunderland, T., 1998. Differential trace amine alterations in individuals receiving acetylenic inhibitors of MAO-A (clorgyline) or MAO-B (selegiline and pargyline). J. Neural. Transm. Suppl. 52, 39–48.

Noh, J.S., Kim, E.Y., Kang, J.S., Kim, H.R., Oh, Y.J., Gwag, B.J., 1999. Neurotoxic and neuroprotective actions of catecholamines in cortical neurons. Exp. Neurol. 159, 217–224.

Olanow, C.W., 1990. Oxidation reactions in Parkinson's disease. Neurology 40, 32–37.

Olivier, V., Gobert, A., Guibert, B., Leviel, V., 1999. The in vivo modulation of dopamine synthesis by calcium ions: influences on the calcium independent release. Neurochem. Int. 35, 431–438.

Osborne, P.G., O'Connor, W.T., Drew, K.L., Ungerstedt, U., 1990. An in vivo microdialysis characterization of extracellular dopamine and GABA in dorsolateral striatum of awake freely moving and halothane anaesthetised rats. J. Neurosci. Methods 34, 99–105.

Paxinos, G., Watson, C., 1998. The Rat Brain in Streotaxic Coordinates. 4th edn. Academic Press, San Diego.

Peters, J.L., Michael, A.C., 2000. Changes in the kinetics of dopamine release and uptake have differential effects on the spatial distribution of extracellular dopamine concentration in rat striatum. J. Neurochem. 74, 1563–1573.

Schneider, J.S., Rothblat, D.S., DiStefano, L., 1994. Volume transmission of dopamine over large distances may contribute to recovery from experimental parkinsonism. Brain Res. 643, 86–91.

Singh, A.K., Banister, E.W., 1981. Relative effects of hyperbaric oxygen on cations and catecholamines metabolism in rats: protection by lithium against seizures. Toxicology 22, 133–147.

Singh, A.K., Banister, E.W., 1983. Tissue ammonia and amino acids in rats at various oxygen pressures. J. Appl. Physiol. 54, 438–444.

Stahle, L., Collin, A.K., Ungerstedt, U., 1990. Effects of halothane anaesthesia on extracellular levels of dopamine, dihydroxyphenylacetic acid, homovanillic acid and 5-hydroxyindolacetic acid in rat striatum: a microdialysis study. Naunyn-Schmiedeberg's Arch. Pharmacol. 342, 136–140.

Tuomainen, P., Tornwall, M., Mannisto, P.T., 1996. Minor effect of tolcapone, a catechol-*o*-methyltransferase inhibitor, on extracellular dopamine levels modified by amphetamine or pargyline: a microdialysis study in anaesthetized rats. Pharmacol. Toxicol. 78, 392–396.

Van Horne, C., Hoffer, B.J., Stromberg, I., Gerhardt, G.A., 1992. Clearance and diffusion of locally applied dopamine in normal and 6-hydroxydopamine lesioned rat striatum. J. Pharmacol. Exp. Ther. 263, 1285–1292.

Vizi, E.S., 1984a. Non-synaptic interactions between neurons modulation of neurochemical transmission. Pharmacological and Clinical Aspects. Wiley, Chichester, NY.

Vizi, E.S., 1984b. Physiological role of cytoplasmic and non-synaptic release of transmitter. Neurochem. Int. 6, 435–440.

Vizi, E.S., 2000. Role of high-affinity receptors and membrane transporters in nonsynaptic communication and drug action in the central nervous system. Pharmacol. Rev. 52, 63–89.

Waldmeier, P.C., Felner, A.E., 1978. Deprenyl, loss of selectivity for inhibition of B-type MAO after repeated treatment. Biochem. Pharmacol. 27, 801–802.

Weber, C.A., Duncan, C.A., Lyons, M.J., Jenkinson, S.G., 1990. Depletion of tissue glutathione with diethyl maleate enhances hyperbaric oxygen toxicity. Am. J. Physiol. 258, L308–L312.

Zetterström, T., Sharp, T., Collin, A.K., Ungerstedt, U., 1988. In vivo measurement of extracellular dopamine and DOPAC in rat striatum after various dopamine-releasing drugs; implications for the origin of extracellular DOPAC. Eur. J. Pharmacol. 148, 327–334.