ELSEVIER

European Journal of Pharmacology 448 (2002) 143–150

www.elsevier.com/locate/ejphar

Tyrosine-induced release of dopamine is under inhibitory control of presynaptic dopamine D2 and, probably, D3 receptors in the dorsal striatum, but not in the nucleus accumbens

Koichi Fusa [a], Tadashi Saigusa [b,c,*], Noriaki Koshikawa [b,c], Alexander R. Cools [d]

[a] *Department of Dental Anaesthesiology, Nihon University School of Dentistry, 1-8-13, Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan*
[b] *Department of Pharmacology, Nihon University School of Dentistry, 1-8-13, Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan*
[c] *Division of Oral and Craniomaxillofacial Research, Dental Research Centre, Nihon University School of Dentistry, 1-8-13, Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan*
[d] *Department of Psychoneuropharmacology, University of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands*

Received 7 March 2002; received in revised form 15 May 2002; accepted 31 May 2002

Abstract

Stimulation of dopamine D2-like receptors decreases extracellular dopamine in the dorsal striatum and the nucleus accumbens. It is unknown whether the role of these receptors differs from that of dopamine D3 receptors. It is also unknown to what extent the role of these two types of receptors varies across both structures. Using microdialysis, we therefore investigated whether intracerebrally administered quinpirole, a dopamine D2-like receptor agonist, and PD 128907, (*S*(+)−(4*aR*,10*bR*)−3,4,4*a*,10*b*−tetrahydro−4−propyl−2*H*,5*H*−[1]−benzopyrano[4,3−*b*]−1,4−oxazin−9−ol, a dopamine D3 receptor preferring agonist, differentially alter the tyrosine-induced increase of extracellular dopamine in the dorsal striatum and the nucleus accumbens, respectively. Perfusion of tyrosine (100 μM) into the dorsal striatum and the nucleus accumbens enhanced extracellular dopamine in a physiological manner in both areas. Infusion of the Na^+ channel blocker tetrodotoxin (2 μM) suppressed the enhanced level of dopamine derived from exogenous tyrosine in both brain areas. Infusion of the dopamine D2-like receptor agonist quinpirole at a concentration (1 nM), which alone did not affect basal extracellular dopamine, reduced tyrosine-enhanced extracellular dopamine when infused into the dorsal striatum, but not into the nucleus accumbens; the preferential dopamine D3 receptor agonist, PD 128907, had similar effects. Haloperidol, a dopamine D2-like receptor antagonist, given systemically at a dose, which alone did not significantly affect basal dopamine levels (10 nmol/kg i.p.), enhanced extracellular dopamine derived from exogenous tyrosine. This haloperidol treatment antagonized only the quinpirole-induced, but not the PD 128907-induced reduction in dopamine levels seen in tyrosine-treated rats. The results show that extracellular dopamine derived from exogenous tyrosine is under inhibitory control of presynaptic dopamine D2-like receptors in the dorsal striatum, but not in the nucleus accumbens; to what extent the same holds for dopamine D3 receptors remains to be proven. Future studies are required to elucidate whether the noted difference is absolute or not.

Keywords: Dopamine; Tyrosine loading, local; Quinpirole; PD 128907; Striatum, dorsal; Nucleus accumbens

1. Introduction

Low doses of the dopamine D2-like receptor agonist quinpirole are known to stimulate presynaptic dopamine receptors and, consequently, to decrease release of dopamine in the striatum and in the nucleus accumbens (Imperato and Di Chiara, 1988; Linthorst et al., 1991, Stamford et al., 1991; See et al., 1991; Svensson et al., 1994; Yamada et al., 1994). It has been suggested that this effect of quinpirole on the release of dopamine should be largely attributed to its affinity for dopamine D3 receptors (Yamada et al., 1994; Gainetdinov et al., 1996), because the effect of quinpirole is more prominent in the nucleus accumbens than in the striatum in in vivo studies (Stamford et al., 1991) as well as in ex vivo studies (Yamada et al., 1994) and because the nucleus accumbens contains a larger number of dopamine D3 receptors than the striatum (Bouthenet et al., 1991; Sokoloff and Schwartz, 1995). On the other hand, it has been suggested that the effect of quinpirole on the synthesis

* Corresponding author. Department of Pharmacology, Nihon University School of Dentistry, 1-8-13, Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan. Tel.: +81-3-3219-8126; fax: +81-3-3219-8136.
E-mail address: saigusa@dent.nihon-u.ac.jp (T. Saigusa).

0014-2999/02/$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
PII: S0014-2999(02)01911-8

of dopamine should be largely attributed to its affinity for dopamine D2 receptors (Gainetdinov et al., 1996), because the magnitude of inhibition of dopamine synthesis via dopamine D2 receptors does not differ between the dorsal striatum and the nucleus accumbens (Gainetdinov et al., 1996) and because dopamine D2 receptors are equally distributed across the dorsal striatum and the nucleus accumbens (Joyce et al., 1991; Boundy et al., 1993; Sokoloff and Schwartz, 1995). However, both in vivo and ex vivo studies (fast cyclic voltametry: Stamford et al., 1988; brain slices: Yamada et al., 1995) have shown that dopamine D2 receptor antagonists produce larger increases of dopamine efflux in the dorsal striatum than in the nucleus accumbens. Although there are some studies in which the effects of intracerebrally administered quinpirole on extracellular dopamine in the striatum or nucleus accumbens have been analysed (Imperato and Di Chiara, 1988; Kalivas and Duffy, 1991; Sarre et al., 1996), so far, there have been no studies in which the effects of intracerebrally administered quinpirole on extracellular dopamine are compared between the dorsal striatum and the nucleus accumbens, implying that it is unknown to what extent these effects are due to interaction with dopamine D2 and/or dopamine D3 receptors. For that reason, the goal of the present study was to investigate whether intracerebrally administered quinpirole, a dopamine D2-like receptor agonist, and PD 128907, (*S*(+)−(4*aR*,10*bR*)−3,4,4*a*,10*b*−tetrahydro−4−propyl−2*H*,5*H*−[1]−benzopyrano[4,3−*b*]−1,4−oxazin−9−ol, a dopamine D3 receptor preferring agonist (Bristow et al., 1996), differentially alter the tyrosine-induced increase of extracellular dopamine in the dorsal striatum and the nucleus accumbens, respectively.

Because increasing the dopamine availability by acute tyrosine loading has been found to elucidate drug-induced changes of extracellular dopamine in the nucleus accumbens (Woods and Meyer, 1991), we used this technique in the present study. A crucial perquisite for assessing this method of acute and local tyrosine loading (100 μM) is that one has to be sure that the extracellular level of dopamine is actually derived from tyrosine inside neurone terminals and released as a result of neuronal activities. In order to exclude the possibility that changes of extracellular dopamine were partially or fully derived from dopamine released by tyramine that is extraneuronally formed from exogenous tyrosine (Nieoullon et al., 1977), we analysed the tetrodotoxin-sensitivity of the tyrosine-induced increase of extracellular dopamine because the tyramine-induced release of dopamine is known to be tetrodotoxin-insensitive (Fairbrother et al., 1990). Because about 10% or less of exogenously applied drugs reaches the extracellular space around the probe (cf. Westerink and De Vries, 2001), the dose of 100 μM tyrosine was expected to result in a level of about 10 μM tyrosine, namely, a level that compares with normal physiological variations in physiological tyrosine levels (cf. Milner and Wurtman, 1985). Once the tetrodotoxin-sensitivity of the tyrosine-induced increase of extracellular dopamine could be established, the ability of the dopamine D2-like receptor agonist quinpirole and the dopamine D3 receptor preferring agonist PD 128907 to reduce extracellular dopamine in the dorsal striatum and nucleus accumbens was studied using doses that per se were unable to affect the extracellular levels of dopamine (1 nM). Finally, the ability of systemically administered haloperidol, a dopamine D2 receptor antagonist, to alter the effects of quinpirole and/or PD 128907 was tested in order to establish the receptor specificity of the observed effects. The dose of haloperidol [10 nmol/kg (3.8 μg/kg) i.p.] was based on earlier published studies (De Boer et al. 1997).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (NRC Haruna, Gunma, Japan) weighing between 200 and 220 g at the start of the experiments were used. These were kept at constant room temperature (23±2 °C) and relative humidity (55±5%) under a 12 h light–dark cycle (light on at 0700 h), with free access to food and water.

2.2. Surgery

Rats were anaesthetised with sodium pentobarbitone (50 mg/kg i.p.). The anaesthetised animals were placed in a stereotactic apparatus, and a guide cannula was implanted just above the left dorsal striatum or the nucleus accumbens [dorsal striatum: antero-posterior (AP) 9.2 mm, medio-lateral (ML) 3.2 mm, dorso-ventral (DV) 7.2 mm; nucleus accumbens: AP 10.6 mm, ML 1.5 mm, DV 4.0 mm from interaural line; Paxinos and Watson, 1986]. To avoid the ventricular system, cannulas directed at the nucleus accumbens were angled at 18° from the mid-sagittal plane. After completion of surgery, rats were allowed to recover for 7–10 days before the experiments were carried out; guide cannulas, 0.4 mm o.d., were kept patented by stainless steel inserts. Each animal was used only once.

The experiments were performed in accordance with institutional guidelines in the care and use of experimental animals that are in compliance with UK Animals (Scientific Procedures) Act, 1986, and all efforts were made to minimise animal suffering, to reduce the number of animals used.

2.3. Dialysis and neurochemical measurements

A commercially available I-shaped removable-type dialysis probe (2 mm length cellulose membrane, 0.22 mm o.d., 50,000 mol. wt. "cut-off", Eicom A-I-8-02 type, Kyoto, Japan) was used. The experiment was started by removing the stylet from the guide cannula and inserting the dialysis

probe, of which just the dialysis tubing protruded from the tip (Fig. 1). The probe was secured to the guide cannula by a screw. Each rat was then placed in a Plexiglas box (30×30×35 cm), inlet and outlet tubes were connected to a swivel located on a counterbalanced beam to minimise discomfort. The probe was perfused at a rate of 2.0 μl/min with modified Ringer's solution (NaCl 147 mM, KCl 4 mM, $CaCl_2$ 1.2 mM, $MgCl_2$ 1.1 mM; pH 7.4) and the outflow connected by Teflon tubing to a high-performance liquid chromatography system (Eicom).

Dopamine was separated on an Eicompak CA-5ODS column (particle size, 5 μm, 2.1×150 mm, Eicom) using phosphate buffer (0.1 M) containing octane-sulfonic acid (3.2 mM), EDTA (0.13 mM) and 20% methanol (pH 6.0) as the mobile phase at a flow rate of 0.23 ml/min. Compounds were quantified by electrochemical detection using a glassy carbon working electrode set at +400 mV against a silver–silver chloride reference electrode (Eicom), giving a detection limit for dopamine of about 0.05 pg per sample. The probes had an in vitro recovery of approximately 12% for dopamine, but the reported concentrations were not adjusted for recovery in vivo because these estimations are inaccurate (Benveniste et al., 1989; Lindefors et al., 1989). Previous experiments in which we have used the same technique and procedure have shown that dopamine efflux is more or less stabilised 4 h after probe insertion, and that levels seen at that time are largely dependent on neuronal release as most of the release is tetrodotoxin-sensitive and Ca^{2+}-dependent (Murai et al., 1994; Takada et al., 1993; Tomiyama et al., 1993, 1995). Perfusate samples were taken every 20 min for quantification of dopamine. Drugs were administered either intraperitoneally or intracerebrally through the dialysis probe at least 4 h after probe insertion. Baseline levels of dopamine were the mean of the last three samples before drug administration and incorporated in the figures.

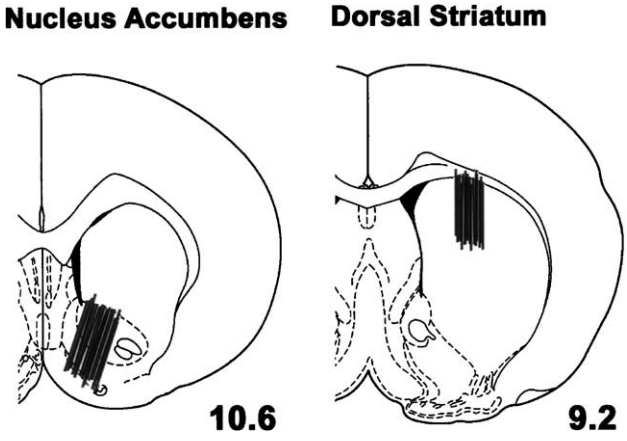

Fig. 1. Schematic illustration showing locations of the probe in the nucleus accumbens (left part) and in the dorsal striatum (right part). The planes are taken from the atlas of Paxinos and Watson (1986), representing anterior distance (mm) from the interaural line.

Detailed behavioural analyses were not included because pilot experiments had shown that none of the given treatments elicited any significant behavioural change.

2.4. Drugs

Drugs used were the dopamine D2-like receptor agonist quinpirole hydrochloride (Research Biochemicals International, Natick, MA, USA), the dopamine D3 receptor preferring agonist PD 128907 (*S*(+)−(4*aR*,10*bR*)−3,4,4*a*,10*b*−tetrahydro-4-propyl-2*H*,5*H*-[1]-benzopyrano[4,3-*b*]-1,4-oxazin-9-ol hydrochloride; Research Biochemicals International), the dopamine precursor L-tyrosine methyl ester hydrochloride (Sigma, St. Louis, MO, USA), the dopamine D2-like receptor antagonist haloperidol (Serenace, Dainippon Pharmaceutical, Osaka, Japan) and the Na^+ channel blocker tetrodotoxin (Sigma). Haloperidol was diluted in 0.9% NaCl solution for intraperitoneal injection, and all intracerebrally administered drugs were dissolved in the modified Ringer's solution that was used for perfusions. Agonists were infused via the dialysis membrane for 20 min, and tyrosine was infused similarly for 60 min commencing together with agonist infusion.

The doses of haloperidol and L-tyrosine were based on the outcome of the studies of De Boer et al. (1997) and Woods and Meyer (1991), respectively. For quinpirole and PD 128907, doses that alone were surely ineffective (1 nM) when administered via dialysis membrane, were chosen on basis of the outcome of the study of Imperato and Di Chiara (1988) in which the effective dose range of quinpirole was found to vary from 100 nM to 10 μM.

2.5. Histology

At the end of each experiment, the rat was deeply anaesthetised with Na^+ pentobarbitone (80 mg/kg, i.p.) and perfused transcardially with 10% formaldehyde solution. The brain was removed, sectioned (50 μm), and stained with cresyl violet to permit probe location.

2.6. Statistical analysis

All values were expressed as a percentage of baseline levels. Comparison of time-course data was performed using two-way analysis of variance (ANOVA) for repeated measures with the factors treatment and time (repeated). Statistical significance was considered to be $P<0.05$.

3. Results

3.1. Histology

Placements of the dialysis probes in the nucleus accumbens and in the dorsal striatum are given in Fig. 1.

3.2. Effects of tetrodotoxin perfusion on the level of dopamine derived from tyrosine infused into the dorsal striatum and the nucleus accumbens

Approximately 4 h after probe insertion, concentrations of dopamine in dialysates of the dorsal striatum [5.4±0.31 pg/20 min (mean±S.E.M., n=63)] and the nucleus accumbens [3.1±0.18 pg/20 min (n=46)] reached a stable baseline value and remained stable over the subsequent 4-h study period. A 60-min infusion of tyrosine (100 μM) significantly elevated extracellular levels of dopamine in the dorsal striatum (F(1,153)=69.45, P<0.001, n=7; Fig. 2A) and in the nucleus accumbens (F(1,143)=16.91, P<0.001, n=8; Fig. 2B). Peak effects of tyrosine occurred approximately 40–80 min after injection onset, being 130% (dorsal striatum) and 125% (nucleus accumbens) of control values.

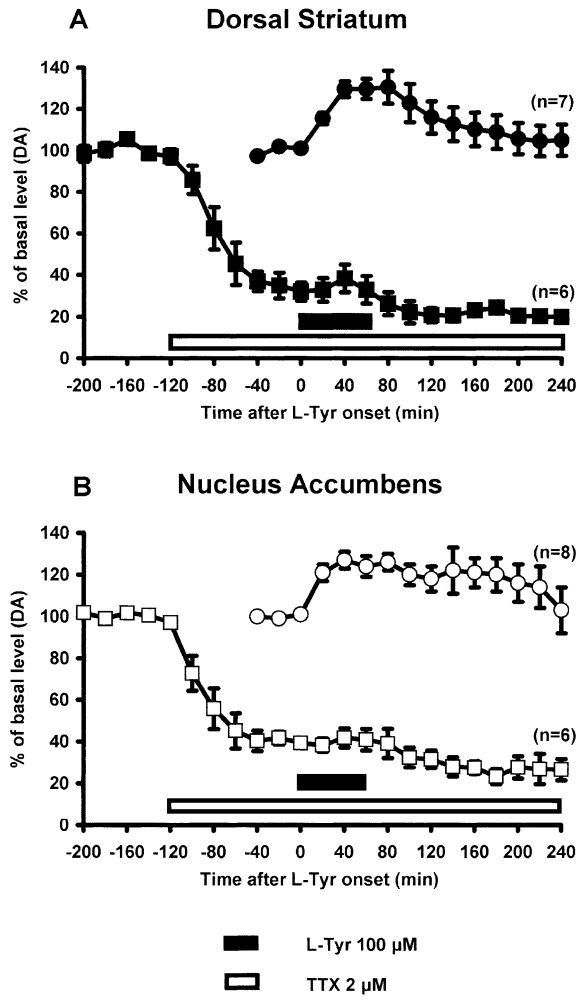

Fig. 2. Effects of L-tyrosine (L-tyr; 100 μM for 60 min) infusion on extracellular levels of dopamine (DA) (upper trace), and effects of tetrodotoxin (2 μM for 360 min) infusion on the levels of DA after L-tyrosine (100 μM for 60 min) infusion (lower trace) into the dorsal striatum (A) and the nucleus accumbens (B).

Tetrodotoxin (2 μM) infused for 2 h via the dialysis probe reduced basal levels of DA by approximately 70% in both the dorsal striatum (n=6) and the nucleus accumbens (n=6) (Fig. 2A,B). This tetrodotoxin infusion almost completely abolished tyrosine-induced enhancement of dopamine levels in both areas (Fig. 2A,B).

3.3. Effects of quinpirole infusion on tyrosine-induced elevation of extracellular dopamine

A 20-min infusion of quinpirole (1 nM) alone into the dorsal striatum (n=5) or the nucleus accumbens (n=7) did not significantly affect extracellular levels of basal dopamine in the respective areas (Fig. 3A,C). Quinpirole infusion suppressed significantly the tyrosine-induced increase of dopamine in the dorsal striatum: this reduction, by about 60% of the area under the curve, was seen for the period of 40–240 min after the start of infusion (F(1,121)=21.74, P<0.001, n=6) (Fig. 3B). A similar infusion of quinpirole into the nucleus accumbens failed to affect tyrosine-induced increase of dopamine (F(1,142)=2.16, P=0.14, n=7; Fig. 3D).

3.4. Effects of PD 128907 infusion on tyrosine-induced elevation of extracellular dopamine

A 20-min infusion of PD 128907 (1 nM) alone into the dorsal striatum (n=5) or the nucleus accumbens (n=5) did not significantly affect extracellular levels of basal dopamine in the respective area (Fig. 4A,C). PD 128907 infusion induced a significant suppression of tyrosine-induced dopamine increase in the dorsal striatum: this effect was present for the period of 40–240 min after the start of infusion (F(1,143)=20.58, P<0.001, n=8; Fig. 4B). A similar infusion of PD 128907 into the nucleus accumbens failed to significantly affect tyrosine-induced increase of dopamine (F(1,142)=0.02, P=0.89, n=7; Fig. 4D).

3.5. Effects of haloperidol on extracellular dopamine derived from exogenous tyrosine in the dorsal striatum and on the quinpirole- and PD 128907-induced reduction

As shown in Fig. 5, haloperidol (10 nmol/kg, i.p., given 2 h before the intracerebral infusion), which itself did not significantly affect basal levels of striatal dopamine (data not shown, n=6), significantly enhanced levels of dopamine in rats that received tyrosine into the dorsal striatum, for the period of 100–240 min after the start of infusion (F(1,88)=54.35, P<0.001; n=6). Such a haloperidol treatment significantly counteracted the quinpirole-induced reduction in dopamine levels for the period of 100–240 min after the start of infusion in tyrosine-treated rats (quinpirole: F(1,80)=17.38, P<0.001, n=6; PD 128907: F(1,96)=43.06, P<0.001, n=6) (Fig. 5). Detailed inspection of the data revealed that not only haloperidol counteracted the effect of quinpirole on tyrosine, but that also quinpirole

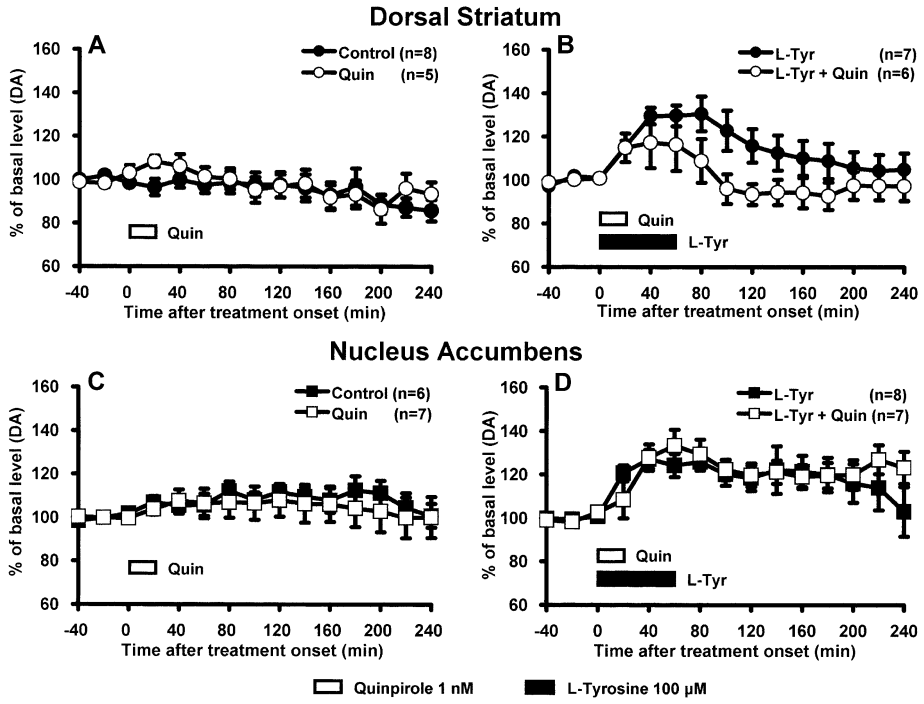

Fig. 3. Effects of quinpirole (quin; 1 nM for 20 min) infusion on basal extracellular levels of dopamine (DA) in the dorsal striatum (A) and the nucleus accumbens (C), and on the L-tyrosine (L-tyr; 100 µM for 60 min)-enhanced extracellular DA levels in the dorsal striatum (B) and the nucleus accumbens (D).

counteracted the effect of haloperidol on that of tyrosine ($F(1,80)=49.13$, $P<0.001$), showing that the chosen dose of haloperidol inhibited the effects of quinpirole. This did not hold for the effects of PD 128907. Although haloperidol reduced the effect of this drug on tyrosine, PD 128907 itself did not counteract the effect of haloperidol on tyrosine: the difference between rats that had received haloperidol, PD 128907 and tyrosine, and rats that had received PD 128907

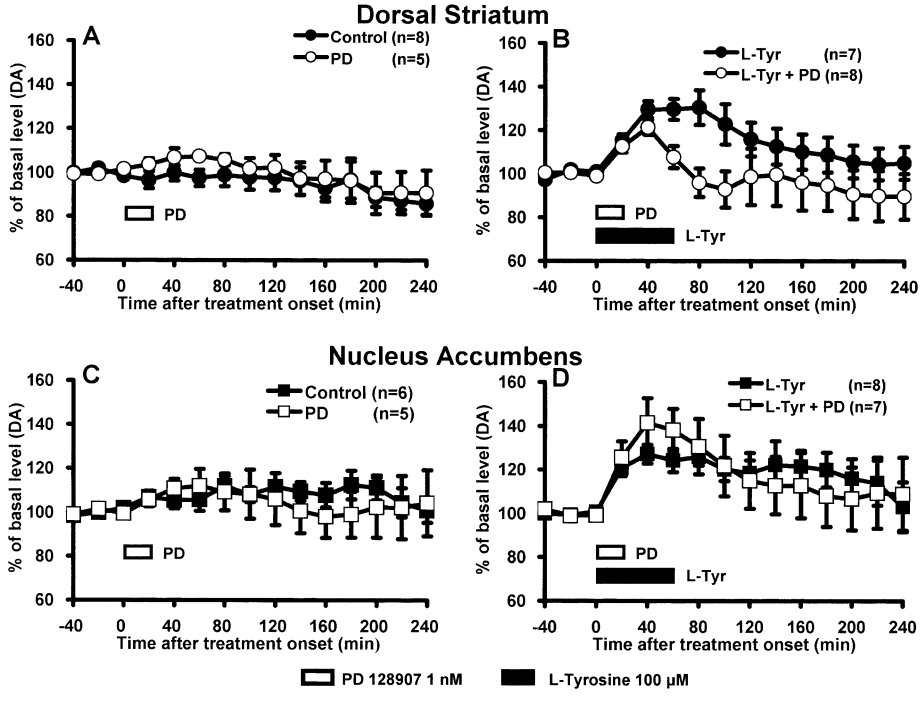

Fig. 4. Effects of PD 128907 (PD; 1 nM for 20 min) infusion on basal extracellular levels of dopamine (DA) in the dorsal striatum (A) and the nucleus accumbens (C), and on the L-tyrosine (L-tyr; 100 µM for 60 min)-enhanced extracellular DA levels in the dorsal striatum (B) and the nucleus accumbens (D).

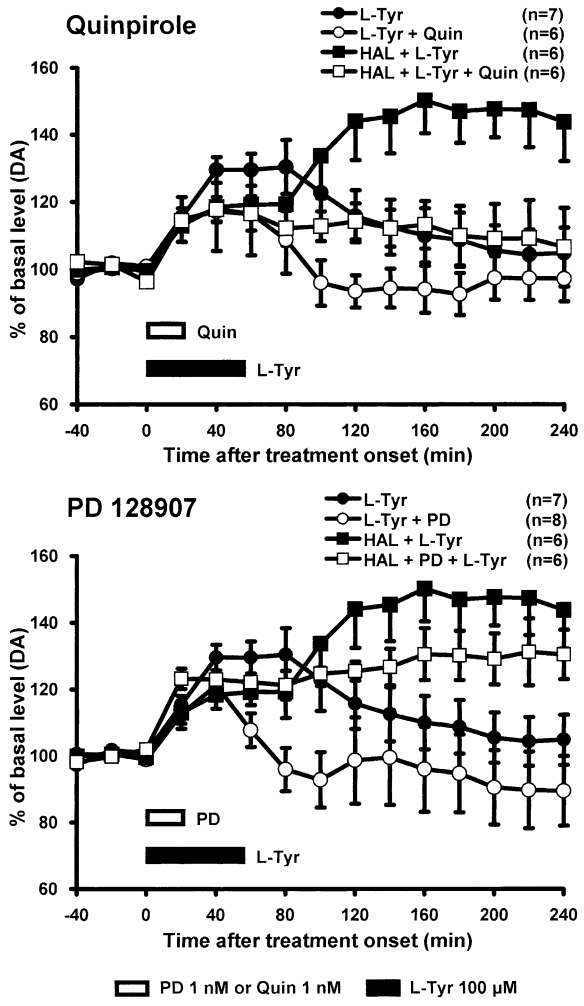

Fig. 5. Effects of haloperidol (HAL; 10 nmol/kg i.p.) on the extracellular levels of dopamine (DA) after L-tyrosine (L-tyr; 100 µM for 60 min) infusion into the dorsal striatum, and on the quinpirole (quin; 1 nM for 20 min; upper panel)-induced or PD 128907 (PD; 1 nM for 20 min; lower panel)-induced reduction in extracellular DA derived from L-tyrosine (100 µM for 60 min) infusion into the dorsal striatum.

and tyrosine was not significantly different from that between rats that had received haloperidol and tyrosine, and rats that had received tyrosine, indicating that the chosen dose of haloperidol did not inhibit PD 128907.

4. Discussion

Infusion of tyrosine at a concentration of 100 µM into the dorsal striatum and the nucleus accumbens for 60 min significantly elevated extracellular levels of dopamine in the respective areas. In the nucleus accumbens, a similar elevation of extracellular levels of dopamine has been reported after infusion of the same concentration of tyrosine (Woods and Meyer, 1991). This tyrosine-induced increase of extracellular levels of dopamine has been suggested to be a valid tool for revealing subtle differences in function of dopamine receptors that regulate synthesis or release of dopamine (Woods and Meyer, 1991), especially because the resulting levels of tyrosine and dopamine remain within normal physiological levels (see Introduction). In fact, this is only true on the condition that it can be shown that the extracellularly measured dopamine is really due to the release of dopamine formed inside the neuron. For that reason, we analysed the tetrodotoxin-sensitivity of the tyrosine-induced changes of extracellular dopamine. The present results clearly demonstrate that infusion of tetrodotoxin (2 µM) almost fully suppressed the enhanced level of dopamine derived from exogenous tyrosine in both brain areas. Thus, the results suggest that, under the present experimental conditions, acutely and locally raised extracellular levels of dopamine with 100 µM tyrosine loading are essentially derived from dopamine released by neuronal activity. Accordingly, this type of tyrosine loading can reliably be employed for studying the putatively differential role of presynaptic dopamine D2 and D3 receptors in regulating the synthesis and/or release of dopamine in striatal structures such as the dorsal striatum and the nucleus accumbens. Under the chosen experimental conditions, infusion of the dopamine D2-like receptor agonist quinpirole at a concentration (1 nM), which alone did not affect basal extracellular dopamine levels, reduced tyrosine-enhanced extracellular dopamine levels when infused into the dorsal striatum, but not into the nucleus accumbens. The preferential dopamine D3 receptor agonist, PD 128907, showed a similar profile. Systemic administration of the dopamine D2-like receptor-selective antagonist haloperidol inhibited only the effects of quinpirole: the effects of rats treated with haloperidol, quinpirole and tyrosine significantly differed both from the effects of rats that were treated with quinpirole and tyrosine, and from the effects of rats that were treated with haloperidol and tyrosine. Thus, the effects of quinpirole can be attributed to the involvement of presynaptic dopamine D2-like receptors in the dorsal striatum. In contrast, the effects of haloperidol in rats that were treated with tyrosine were identical to those of haloperidol in rats that were treated with PD 128907 and tyrosine. In other words, haloperidol did not inhibit the effects of PD 128907, indicating that dopamine D2-like receptors were not involved in the effects of PD 128907.

The outcome of the present study reveals two important new findings. The first finding is that the dopamine D3 receptor preferring agonist PD 128907 is able to mimic the effects of the dopamine D2-like receptor agonist quinpirole on the tyrosine-induced increase of extracellular dopamine: it just inhibited the tyrosine-induced increase of dopamine in the dorsal striatum, but not in the nucleus accumbens. In contrast to quinpirole, however, the dopamine D2-like receptor antagonist haloperidol was unable to inhibit these effects, indicating that the effects of PD 128907 were unlikely mediated by dopamine D2-like receptors in the dorsal striatum; this finding opens the perspective that these

were mediated by dopamine D3 receptors in vivo. However, as long as selective dopamine D3 receptor antagonists are not yet available, this hypothesis remains to be tested. It is evident that dose–effect studies are necessary to elucidate whether the noted difference between both brain structures is absolute or not: in the latter case, it is expected that larger doses of the dopamine receptor agonists are required to elicit changes of extracellular dopamine in the nucleus accumbens of tyrosine loaded animals.

Second, this study shows that the outcome of studies in which drugs are intracerebrally administered can fully differ from studies in which the same drugs are systemically administered. In contrast to studies showing that systemically administered quinpirole is less potent in the dorsal striatum than in the nucleus accumbens (see Introduction), our study shows precisely the mirror image: intracerebrally administered quinpirole is far more potent in the dorsal striatum than in the nucleus accumbens in which it actually remains devoid of any effect. Yamada et al. (1995) who used brain slices, have also reported that dopamine D2-like receptor antagonists are more potent in the dorsal striatum than in the nucleus accumbens. These distinct outcomes are fully understandable in view of the fact that systemically administered drugs act at a variety of sites, varying from postsynaptic sites to autaptic sites, whereas in our experimental paradigm as well as in that of Yamada et al. (1995), the drugs could only elicit their effects via interaction with presynaptic receptors that regulate the release and/or synthesis of dopamine. The impact of this insight is that conclusions about the involvement of a particular type of dopamine receptor cannot be based on the outcome of studies in which the drugs are systemically applied. In other words, studies in which the effects of locally applied drugs are studied, are required for drawing conclusions about the degree in which a particular group of receptors is involved in the effects observed. Thus, the present study provides the original evidence that presynaptic dopamine D2 receptors in the dorsal striatum play a more important role in regulating extracellular dopamine than these receptors in the nucleus accumbens do.

In conclusion, the present study shows that the tyrosine-induced increase of extracellular levels of dopamine essentially reflect physiological dopamine release resulting from neuronal activity. Moreover, the present study provides direct evidence that presynaptic dopamine D2-like receptors in the dorsal striatum play a more important role in regulating extracellular dopamine than these receptors in the nucleus accumbens do. Finally, the present study shows that PD 128907 mimics the effects of quinpirole on the tyrosine-induced increase of dopamine, although this effect could not be inhibited by haloperidol, implying that not dopamine D2-like receptors, but dopamine D3 receptors might be involved in the effects of PD 128907 in the dorsal striatum. As long as selective dopamine D3 receptor antagonists are not yet available, this hypothesis remains to be tested.

Acknowledgements

This study was supported by Research Grants from the Sato Fund (T.S.), Uemura Fund (T.S.), and Dental Research Centre (N.K.), Nihon University School of Dentistry; an Individual Research Grant from Nihon University (T.S.); a grant for promotion of multidisciplinary research project from the Ministry of Education, Culture, Sports, Science and Technology, Japan (N.K., A.R.C.); and The Promotion and Mutual Aid Corporation for Private School of Japan (K.F., N.K.). The authors thank Takafumi Morishita and Hiroko Okutsu for their help with the dialysis experiments.

References

Benveniste, H., Hansen, A.J., Ottosen, N.S., 1989. Determination of brain interstitial concentrations by microdialysis. J. Neurochem. 52, 1741–1750.

Boundy, V.A., Luedtke, R.R., Artymyshyn, R.P., Filtz, T.M., Molinoff, P.B., 1993. Development of polyclonal anti-D2 dopamine receptor antibodies using sequence-specific peptides. Mol. Pharmacol. 43, 666–676.

Bouthenet, M.-L., Souil, E., Martres, M.-P., Sokoloff, P., Giros, B., Schwartz, J.-C., 1991. Localization of dopamine D_3 receptor mRNA in the rat brain using in situ hybridization histochemistry: comparison with dopamine D_2 receptor mRNA. Brain Res. 564, 203–219.

Bristow, L.J., Cook, G.P., Gay, J.C., Kulagowski, J.J., Landon, L., Murray, F., Saywell, K.L., Young, L., Hutson, P.H., 1996. The behavioural and neurochemical profile of the putative dopamine D3 receptor agonist, (+)−PD 128907, in the rat. Neuropharmacology 35, 285–294.

De Boer, P., Enrico, P., Wright, J., Wise, L.D., Timmerman, W., Moor, E., Dijkstra, D., Wikstrom, H.V., Westerink, B.H., 1997. Characterization of the effect of dopamine D3 receptor stimulation on locomotion and striatal dopamine levels. Brain Res. 758, 83–91.

Fairbrother, I.S., Arbuthnott, G.W., Kelly, J.S., Butcher, S.P., 1990. In vivo mechanisms underlying dopamine release from rat nigrostriatal terminals: II. Studies using potassium and tyramine. J. Neurochem. 54, 1844–1851.

Gainetdinov, R.R., Sotnikova, T.D., Grekhova, T.V., Rayevsky, K.S., 1996. In vivo evidence for preferential role of dopamine D_3 receptor in the presynaptic regulation of dopamine release but not synthesis. Eur. J. Pharmacol. 308, 261–269.

Imperato, A., Di Chiara, G., 1988. Effects of locally applied D-1 and D-2 receptor agonists and antagonists studied with brain dialysis. Eur. J. Pharmacol. 156, 385–393.

Joyce, J.N., Janowsky, A., Neve, K.A., 1991. Characterization and distribution of [^{125}I]epidepride binding to dopamine D2 receptors in basal ganglia and cortex of human brain. J. Pharmacol. Exp. Ther. 257, 1253–1263.

Kalivas, P.W., Duffy, P., 1991. A comparison of axonal and somatodendritic dopamine release using in vivo dialysis. J. Neurochem. 56, 961–967.

Lindefors, N., Amberg, G., Ungerstedt, U., 1989. Intracerebral microdialysis: I. Experimental studies of diffusion kinetics. J. Pharmacol. Methods 22, 141–156.

Linthorst, A.C.E., De Lang, H., De Jong, W., Versteeg, D.H.G., 1991. Effect of the dopamine D_2 receptor agonist quinpirole on the in vivo release of dopamine in the caudate nucleus of hypertensive rats. Eur. J. Pharmacol. 201, 125–133.

Milner, J.D., Wurtman, R.J., 1985. Tyrosine availability determines stimulus-evoked dopamine release from rat striatal slices. Neurosci. Lett. 59, 215–220.

Murai, T., Koshikawa, N., Kanayama, T., Takada, K., Tomiyama, K., Kobayashi, M., 1994. Opposite effects of midazolam and beta-carboline-3-carboxylate ethyl ester on the release of dopamine from rat nucleus

accumbens measured by in vivo microdialysis. Eur. J. Pharmacol. 261, 65–71.

Nieoullon, A., Cheramy, A., Glowinski, J., 1977. An adaptation of the push–pull cannula method to study the in vivo release of (^{3}H)dopamine synthesized from (^{3}H)tyrosine in the cat caudate nucleus: effects of various physical and pharmacological treatments. J. Neurochem. 28, 819–828.

Paxinos, G., Watson, C., 1986. The Rat Brain in Stereotaxic Coordinates. Academic Press, New York.

Sarre, S., Ebinger, G., Michotte, Y., 1996. Levodopa biotransformation in hemi-Parkinson rats: effect of dopamine receptor agonists and antagonists. Eur. J. Pharmacol. 296, 247–260.

See, R.E., Sorg, B.A., Chapman, M.A., Kalivas, P.W., 1991. In vivo assessment of release and metabolism of dopamine in the ventrolateral striatum of awake rats following administration of dopamine D_1 and D_2 receptor agonists and antagonists. Neuropharmacology 30, 1269–1274.

Sokoloff, P., Schwartz, J.C., 1995. Novel dopamine receptors half a decade later. Trends Pharmacol. Sci. 16, 270–275.

Svensson, K., Carlsson, A., Huff, R.M., Kling-Petersen, T., Waters, N., 1994. Behavioral and neurochemical data suggest functional differences between dopamine D_2 and D_3 receptors. Eur. J. Pharmacol. 263, 235–243.

Stamford, J.A., Kruk, Z.L., Millar, J., 1988. Actions of dopamine antagonists on stimulated striatal and limbic dopamine release: an in vivo voltammetric study. Br. J. Pharmacol. 94, 924–932.

Stamford, J.A., Kruk, Z.L., Millar, J., 1991. Differential effects of dopamine agonists upon stimulated limbic and striatal dopamine release: in vivo voltammetric data. Br. J. Pharmacol. 102, 45–50.

Takada, K., Murai, T., Kanayama, T., Koshikawa, N., 1993. Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by in vivo microdialysis. Br. J. Anaesth. 70, 181–185.

Tomiyama, K., Noguchi, M., Koshikawa, N., Kobayashi, M., 1993. YM-09151-2 but not l-sulpiride induces transient dopamine release in rat striatum via a tetrodotoxin-insensitive mechanism. J. Neurochem. 60, 1690–1695.

Tomiyama, K., Koshikawa, N., Funada, K., Oka, K., Kobayashi, M., 1995. In vivo microdialysis evidence for transient dopamine release by benzazepines in rat striatum. J. Neurochem. 65, 2790–2795.

Westerink, B.H., De Vries, J.B., 2001. A method to evaluate the diffusion rate of drugs from a microdialysis probe through brain tissue. J. Neurosci. Methods 109, 53–58.

Woods, S.K., Meyer, J.S., 1991. Exogenous tyrosine potentiates the methylphenidate-induced increase in extracellular dopamine in the nucleus accumbens: a microdialysis study. Brain Res. 560, 97–105.

Yamada, S., Yokoo, H., Nishi, S., 1994. Differential effects of dopamine agonists on evoked dopamine release from slices of striatum and nucleus accumbens in rats. Brain Res. 648, 176–179.

Yamada, S., Takaki, T., Yokoo, H., Tanaka, M., 1995. Differential effects of dopamine antagonists on evoked dopamine release from slices of striatum and nucleus accumbens in rats. J. Pharm. Pharmacol. 47, 259–262.