British Journal of Pharmacology (1995) 116, 1545–1550

5-HT_3 receptor agonist induced carrier-mediated release of dopamine in rat striatum *in vivo*

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1 *In vivo* microdialysis was used to study the effect of phenylbiguanide (PBG), a 5-hydroxytryptamine$_3$ receptor agonist, on the extracellular output of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in the corpus striatum.

2 PBG produced a dose-related (10–500 μM) increase in the release of dopamine (280–2000%). DOPAC and HVA output decreased with the perfusion of PBG. This decrease was similar with 50–500 μM PBG. 5-HIAA output was not affected by any PBG concentration used.

3 When nomifensine (5 μM) was included in the Ringer solution, the effect of PBG on the release of dopamine was ameliorated or inhibited. However, the effect of PBG (50–500 μM) on the extracellular output of DOPAC and HVA was similar in the absence and in the presence of nomifensine (5 μM).

4 Perfusion of MDL 72222, a 5-hydroxytryptamine$_3$ receptor antagonist, at doses of 50 and 100 μM produced similar decreases (50% of controls) and increases (120% of controls) in the extracellular output of dopamine and DOPAC, respectively. HVA and 5-HIAA output levels were not affected by either concentration of MDL 72222. MDL 72222 (10 μM) produced a slight and transient increase in the release of dopamine and a decrease in the extracellular output of DOPAC. HVA and 5-HIAA extracellular output was not affected by MDL 72222 (10 μM) perfusion.

5 Co-perfusion of MDL 72222 (10 and 100 μM) or tetrodotoxin (1 μM) with PBG (50 μM) did not modify the effect produced by PBG (50 μM) alone on the release of dopamine.

6 These results suggest that the effect of PBG on the release of dopamine is mainly carrier-mediated.

Keywords: Dopamine; 5-HT_3 receptors; phenylbiguanide; microdialysis; striatum

Introduction

Within the basal ganglia, a host of anatomical, electrophysiological and biochemical data suggest an important functional interplay between central 5-hydroxytryptamine (5-HT) and dopamine pathways (de Simoni *et al.*, 1987). 5-HT induces changes in dopamine release *in vitro* (Blandina *et al.*, 1988) and *in vivo* (Jiang *et al.*, 1990; Benloucif & Galloway, 1991; Chen *et al.*, 1991). The influence of 5-HT on dopaminergic function is enigmatic, since *in vitro* incubation of striatal slices or synaptosomes with 5-HT agonists has been shown both to inhibit and facilitate dopamine release (de Belleroche & Bradford, 1980; Ennis *et al.*, 1981; Westfall & Tittermary, 1982; Hetey & Drescher, 1986; Blandina *et al.*, 1988; Muramatsu *et al.*, 1988). The fact that local infusion of 5-HT facilitates dopamine release from dopamine nerve terminals (Galloway *et al.*, 1993) contrasts with the absence of an effect of systemically administered 5-HT agents on dopamine cell firing (Kelland *et al.*, 1990) or striatal dopamine levels (Perry & Fuller, 1992).

Several *in vitro* studies with radiolabelled dopamine maintain that the effects of 5-HT agonists (e.g. phenylbiguanide, PBG) are mediated via the dopamine transporter (Schmidt & Black, 1989; Yi *et al.*, 1991; Benuck & Reith, 1992; Jacocks & Cox, 1992), whereas Blandina *et al.* (1989) suggest that the effect occurs via a 5-HT_3 receptor-mediated mechanism. Therefore, the exact nature of this interaction remains controversial. The idea that in some instances dopamine release was dependent on the action of the uptake carrier seemed to us to be worthy of a direct test *in vivo*.

We investigated by microdialysis the effect of a selective 5-HT_3 receptor agonist, PBG (Hoyer, 1989), on the extracellular output of dopamine, its metabolites (3,4-dihydroxyphenylacetic acid, DOPAC, and homovanillic acid, HVA) and 5-hydroxyindoleactic acid (5-HIAA) in the rat striatum alone or co-perfused with a dopamine reuptake blocker (nomifensine), a selective 5-HT_3 receptor antagonist (MDL 72222) (Fozard, 1984) or a sodium channel blocker (tetrodotoxin).

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Methods

Animals and drug treatment

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

The following drugs were dissolved in the perfusion fluid: nomifensine maleate, 1-phenylbiguanide (N-phenyl-imidodicarbonimidic diamide) and MDL 72222 (3-tropanyl-3,5-dichlorobenzoate) (Research Biochemical Inc., Natick, MA, U.S.A.), and tetrodotoxin (Sigma Chemical Co., St. Louis, MO, U.S.A.).

Surgery and brain dialysis

Microdialysis in the corpus striatum was performed with an I-shaped cannula (Santiago & Westerink, 1990). The exposed tip of the dialysis membrane was 4 mm. The dialysis tube (i.d.: 0.22 mm; o.d.: 0.31 mm) was prepared from polyacrylonitrile/sodium methalyl sulphonate copolymer (AN 69, Hospal, Bologna, Italy). The *in vitro* recovery of the membrane ($n=5$) was: 22.1 ± 1.8%, for dopamine; 30.2 ± 2.9%, for 3,4-dihydroxyphenylacetic acid (DOPAC); 29.7 ± 2.6%, for homovanillic acid (HVA); and 27.3 ± 2.2%, for 5-hydroxyindoleacetic acid (5-HIAA). The probe was implanted into the corpus striatum [A/P 0.6, L/M 2.8, V/D 6.0, from bregma point and dura] during general chloral hydrate (400 mg kg^{-1}, i.p.) and local lignocaine (10% w/v in water) anaesthesia.

The perfusion experiments were carried out 24–48 h after implantation of the probe. Brain dialysis was performed with a fully automated on-line system as has been described pre-

viously (Westerink *et al.*, 1987a). In brief, two polyethylene tubes (i.d. = 0.28 mm) were connected to the outlets of the dialysis tube. One tube (45 cm in length) was connected to the perfusion pump, and the other (45 cm in length) to the injection valve of the high performance liquid chromatography (h.p.l.c.) apparatus. From the time drugs were included in the Ringer solution (delivered by the perfusion pump) to the time when the first sample with drugs was injected onto the column, there was a lag time of about 30 min; the data presented are corrected to account for this lag time. With the help of an electronic timer, the injection valve was held in the load position for 15 min, during which the sample loop (40 μl) was filled with dialysate. The valve then switched automatically to the injection position for 15 s. This procedure was repeated every 15 min, the time needed to record a complete chromatogram. The corpus striatum was perfused with Ringer solution at a flow rate of 3.0 μl min^{-1} (perfusor VI, B. Braun, Melsungen, Germany). The composition of the Ringer solution was (in mM): NaCl 140, KCl 4.0, $CaCl_2$ 1.2 and $MgCl_2$ 1.0. At the end of the experiment, the rat was given an overdose of chloral hydrate, and the brain was fixed with 4% paraformaldehyde via intracardiac perfusion. Coronal sections (40 μm thick) were made, and dialysis probe placement localized according to the atlas of Paxinos & Watson (1986).

Chemical assays

Dopamine, DOPAC, HVA and 5-HIAA were quantitated by h.p.l.c. with electrochemical detection. A Kontron 420 pump was used in conjunction with a glassy carbon electrode set at −780 mV (ANTEC, The Netherlands). A Merck Lichrocart cartridge (125 mm × 4 mm) column filled with Lichrospher reverse-phase C_{18} 5 μm material was used. The mobile phase consisted of a mixture of 0.05 M of sodium acetate, 0.4 mM of 1-octanesulphonic acid, 0.3 mM of Na_2EDTA and 70 ml methanol l^{-1} adjusted to pH 4.1 with acetic acid. The flow rate was 0.8 ml min^{-1} and the detection limit for dopamine, DOPAC, HVA and 5-HIAA was 5, 5, 20 and 25 fmol per injection, respectively.

Expression of results and statistics

The average of the last four stable samples before drug-treatment was used as a basal value and was defined as 100%. All values given are expressed as percentages of basal values. Difference between the average dialysate concentrations of the basal values and drugs treatment was compared by Kruskal-Wallis analysis of variance by ranks, and, where appropriate (H value greater than the 95% confidence level), means were compared by the Mann-Whitney U-test. Student's *t* test was used to compare data without and with nomifensine, MDL 72222 or TTX at the same collection time.

Results

Among the different experiments carried out in the present study, extracellular basal values were similar and as follows (in fmol min^{-1}, $n = 20-25$): dopamine, 14.7 ± 0.9 and 120.5 ± 9.3, in the absence and in the presence of 5 μM nomifensine, respectively; DOPAC, 1497.0 ± 71.5 (24 h after surgery) and 568.3 ± 40.3 (48 h after surgery); HVA, 1481.4 ± 62.5 (24 h after surgery) and 637.7 ± 41.0 (48 h after surgery); and 5-HIAA, 1322.5 ± 51.7 (24 h after surgery) and 885.4 ± 39.0 (48 h after surgery). The PBG dose-response curve is depicted in Figure 1. The concentration of PBG used ranged from 10 to 500 μM, producing an increase in the release of dopamine in the range 280 to 2000% (Figure 1a). DOPAC (Figure 1b) and HVA (Figure 1c) extracellular output decreased during and after the perfusion of PBG, producing similar effects at the different concentrations of PBG studied. 5-HIAA extracellular output was not affected by PBG perfusion at any concentration studied (data not shown).

Next, we studied the differences in the effect of PBG in the absence and in the presence of nomifensine (5 μM) on the release of dopamine (Figure 2). The presence of the dopamine reuptake blocker ameliorated or inhibited the effect that PBG produced on the release of dopamine. However, the presence of nomifensine did not produce any significant change on the effect produced by PBG on the extracellular output of DOPAC (Figure 3) and HVA (Figure 4), with the exception of the effect of 10 μM PBG on DOPAC extracellular output (Figure 3a). 5-HIAA output remained unchanged in all the conditions studied (data not shown).

Perfusion of the 5-HT_3 receptor antagonist, MDL 72222, at the lowest concentration studied (10 μM), did not produce any significant effect on the striatal extracellular output of dopamine (Figure 5a), DOPAC (Figure 5b), HVA (Figure 5c) or 5-HIAA (data not shown). However, higher doses of MDL

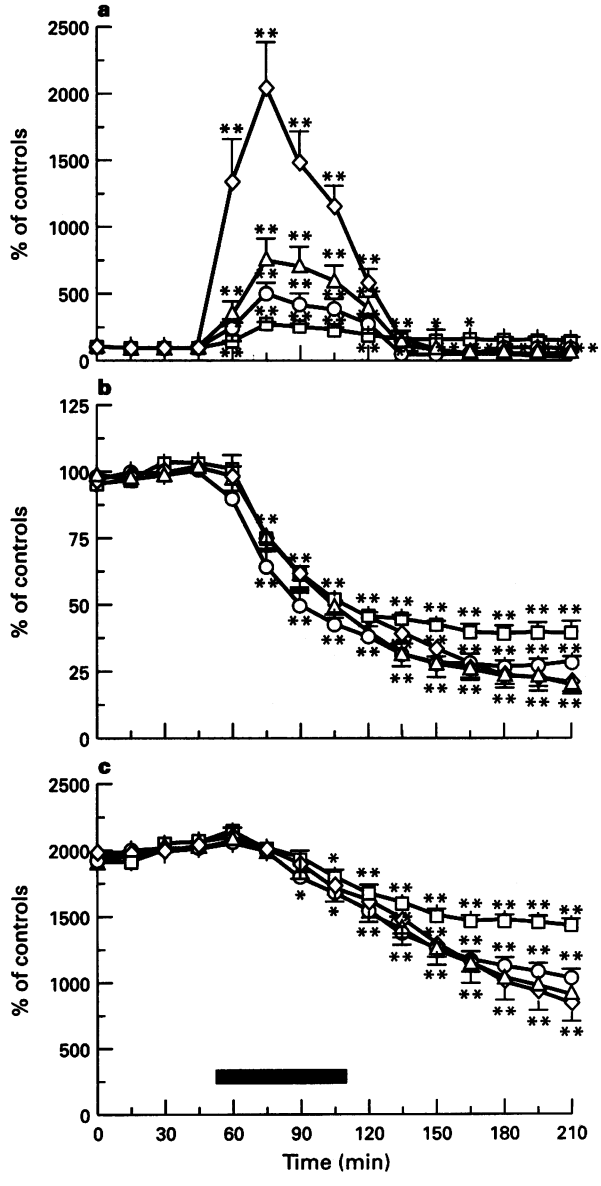


Figure 1 Effect of the perfusion (solid horizontal bar) of phenylbiguanide 10 (□, $n = 5$), 50 (○ $n = 4$), 100 (△ $n = 6$) and 500 μM (◇ $n = 5$) on the extracellular output of dopamine (a), DOPAC (b) and HVA (c) in the corpus striatum. The data are means ± s.e.mean values, expressed as percentages of the controls. Statistical significance (Kruskal-Wallis followed by Mann-Whitney's test): $^{*}P < 0.05$; $^{**}P < 0.01$, compared with the control value.

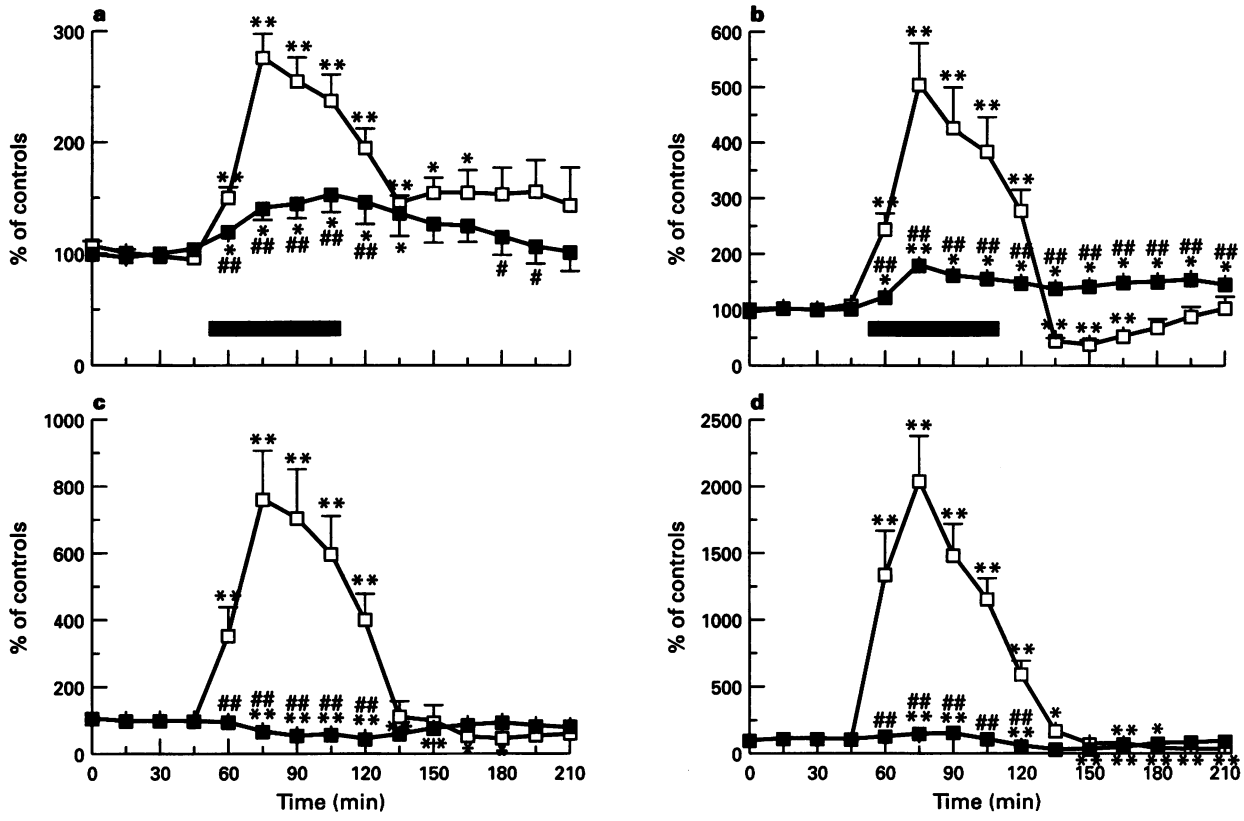
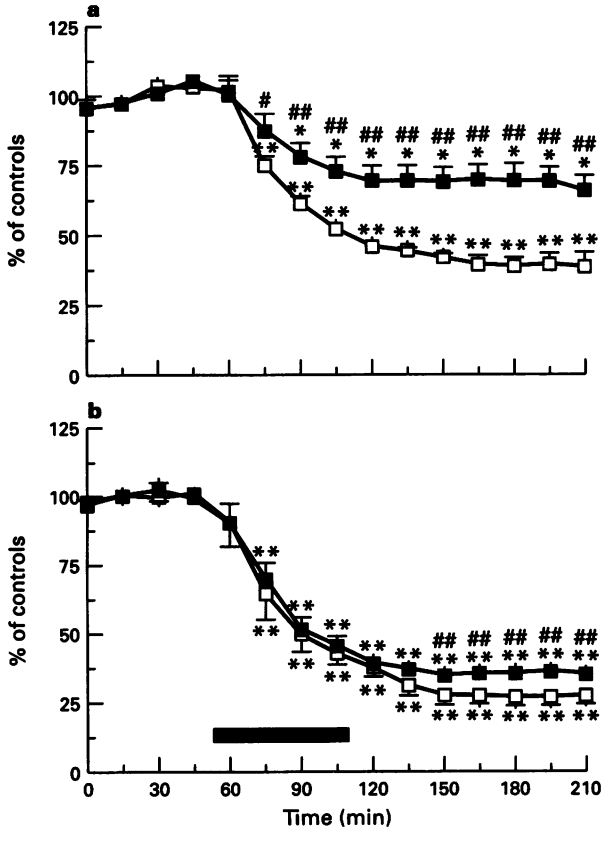


Figure 2 Effect of the perfusion (solid horizontal bar) of phenylbiguanide 10 (a) 50 (b), 100 (c) and 500 μM (d) on the release of dopamine in the absence (□) and in the presence (■) of nomifensine (5 μM) in the corpus striatum. The data are means ± s.e.mean values, expressed as percentages of the controls ($n=4-6$). Statistical significance (Kruskal-Wallis followed by Mann-Whitney's test): $^{*}P<0.05$; $^{**}P<0.01$, compared with the control value. $^{\#\#}P<0.01$, comparing data without and with nomifensine at the same collection time (Student's t test).



72222 (50 and 100 μM) produced similar decreases (50% of controls) and increases (120% of controls) in the extracellular output of dopamine (Figure 5a) and DOPAC (Figure 5b), respectively. HVA (Figure 5c) and 5-HIAA (data not shown) extracellular output were not affected by either of the MDL 72222 concentrations.

Figure 6 shows that co-perfusion of MDL 72222 (10 and 100 μM) with PBG (50 μM) did not modify the effect produced on the release of dopamine by PBG (50 μM) alone. MDL 72222 perfusion started 30 min before its co-perfusion with PBG. DOPAC, HVA and 5-HIAA extracellular output was similar in the presence and in the absence of MDL 72222 (10 and 100 μM) in the Ringer solution (data not shown).

Finally, co-perfusion of tetrodotoxin (TTX, 1 μM) with PBG (50 μM) is shown in Figure 7. TTX alone produced a marked decrease in the release of dopamine. However, when PBG was included in the Ringer perfusion along with TTX, an increase in the release of dopamine, similar to the effect without TTX, was found. Output of DOPAC, HVA or 5-HIAA was not affected by this treatment (data not shown).

Figure 3 Effect of the perfusion (solid horizontal bar) of phenylbiguanide 10 (a) and 50 μM (b) on the extracellular output of DOPAC in the absence (□) and in the presence (■) of nomifensine (5 μM) in the corpus striatum ($n=4-6$). The data are means ± s.e.mean values, expressed as percentages of the controls. Statistical significance (Kruskal-Wallis followed by Mann-Whitney's test): $^{*}P<0.05$; $^{**}P<0.01$, compared with the control value. $^{\#}P<0.05$; $^{\#\#}P<0.01$, comparing data without and with nomifensine at the same collection time (Student's t test).

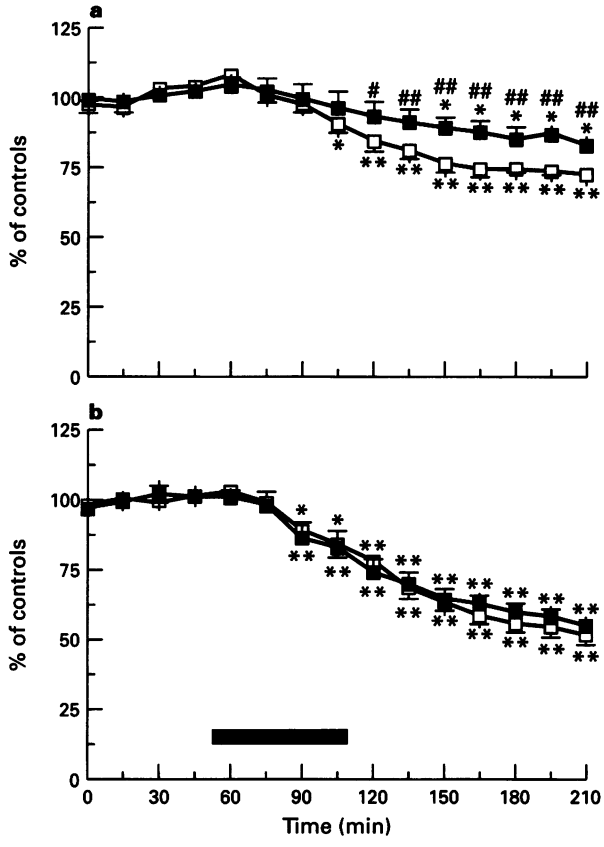


Figure 4 Effect of the perfusion (solid horizontal bar) of phenylbiguanide 10 (a) and 50 μM (b) on the extracellular output of HVA in the absence (□) and in the presence (■) of nomifensine (5 μM) in the corpus striatum. The data are means ± s.e.mean values, expressed as percentages of the controls ($n=4-6$). Statistical significance (Kruskal-Wallis followed by Mann-Whitney's test): $^{*}P<0.05$; $^{**}P<0.01$, compared with the control value. $^{\#}P<0.05$; $^{\#\#}P<0.01$, comparing data without and with nomifensine at the same collection time (Student's t test).

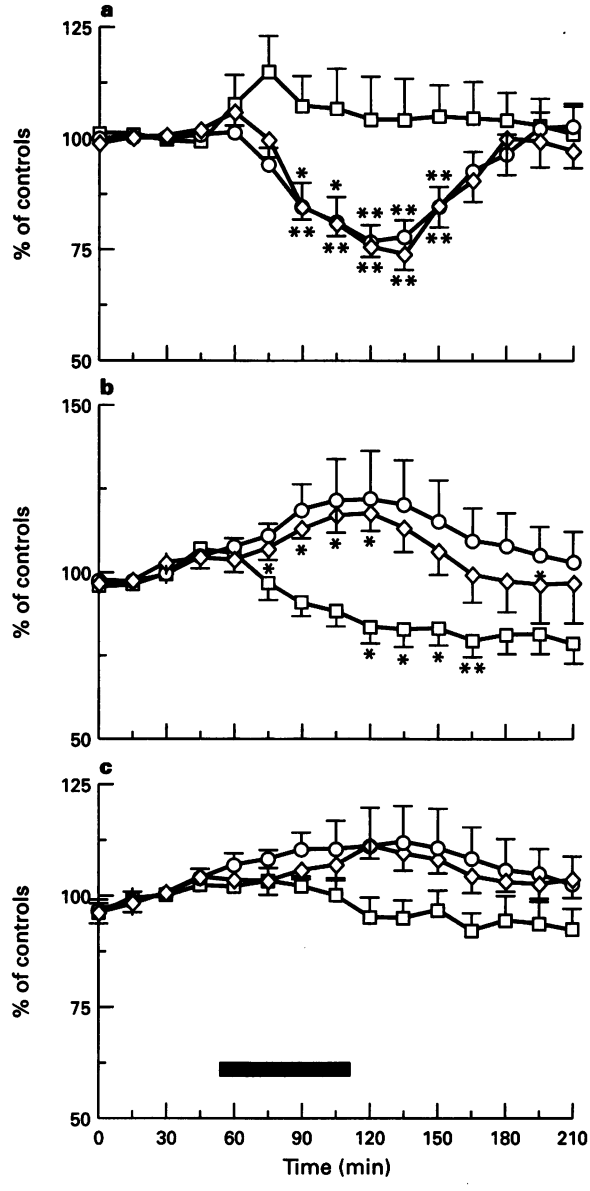


Figure 5 Effect of the perfusion (solid horizontal bar) of MDL 72222 10 (□, $n=6$), 50 μM (○, $n=6$) and 100 μM (◇, $n=6$) on the extracellular output of dopamine (a), DOPAC (b) and HVA (c) in the corpus striatum. The data are means ± s.e.mean values, expressed as percentages of the controls. Statistical significance (Kruskal-Wallis followed by Mann-Whitney's test): $^{*}P<0.05$; $^{**}P<0.01$, compared with the control value.

Discussion

The present study shows that perfusion of 5-HT$_3$ receptor agonist, phenylbiguanide (PBG), produces an increase in the *in vivo* release of dopamine in a dose dependent manner in the striatum. This effect has also been reported in striatal slices (Schmidt & Black, 1989) and in the nucleus accumbens by microdialysis (Chen *et al.*, 1991). However, there is some controversy regarding the interpretation of the results. The former study suggests that some portion of the *in vitro* effect of 5-HT on the release of dopamine may not be 5-HT receptor-mediated. In contrast, the latter group suggests that there is a potent modulation of dopamine release in the nucleus accumbens mediated via 5-HT$_3$ receptors presynaptically localized on dopamine terminals.

In our study, a high concentration of PBG produced a marked increase in the release of dopamine, which is difficult to reconcile with the relatively low density of 5-HT$_3$ receptor binding reported in the striatum (Kilpatrick *et al.*, 1989; Waeber *et al.*, 1989). Since carrier-mediated release of monoamines is a frequently observed phenomena, the possibility that the effect of PBG on dopamine release occurs through a dopamine transporter, prompted us to include in the Ringer perfusion a dopamine reuptake blocker, 5 μM nomifensine, during the whole of the PBG (10–500 μM) experiment. The combined administration of phenylbiguanide with nomifensine abolished or ameliorated the effect of PBG on the release of dopamine. Moreover, a selective 5-HT$_3$ receptor antagonist, MDL 72222 (10 and 100 μM), did not antagonize the effect produced by PBG (50 μM). Martin *et al.* (1992) have reported that the effect of 2-methyl-5-HT (0.1–10 μM), a selective 5-HT$_3$ receptor agonist, on hippocampal *in vivo* 5-HT release was abolished by concurrent perfusion of a low dose of MDL 72222 (1 μM).

Our data suggest that PBG can induce a release of dopamine via a carrier-dependent process, which could be unrelated to receptor activation. Curiously, 2-methyl-5-HT, a 5-HT$_3$ receptor agonist, induced release of dopamine in rat striatal slices apparently independent of the impulse flow (Blandina *et al.*, 1988). Likewise, it has recently been observed that systemic administration of the 5-HT receptor agonist increases extracellular dopamine (Galloway *et al.*, 1993) with little effect on dopamine neuronal firing rate (Kelland *et al.*, 1990).

The hypothesis that PBG increases dopamine release through the dopamine transporter is further confirmed with the use of the neurotoxin, tetrodotoxin (TTX). As TTX is known to block the sodium conductance, we co-perfused TTX with PBG. This offered the possibility of establishing whether neuronal activity is or is not involved in the PBG-induced re-

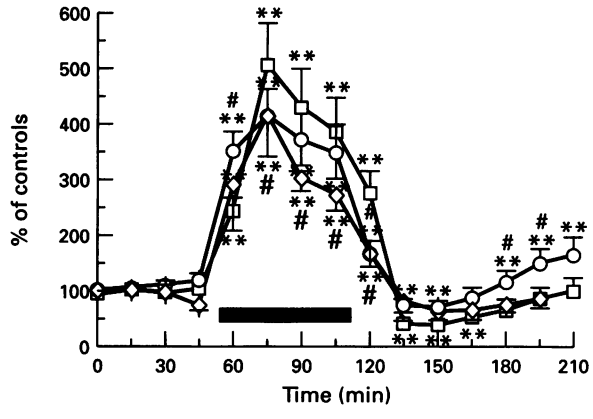


Figure 6 Effect of the perfusion (solid horizontal bar) of phenylbiguanide (50 μM) (□, $n=4$) and co-perfusion of phenylbiguanide (50 μM) with MDL 72222 (10 μM) (○, $n=6$) and 100 μM (◇, $n=6$) on the extracellular output of dopamine in the corpus striatum. MDL 72222 (10 and 100 μM) perfusion started 30 min before its co-perfusion with phenylbiguanide (50 μM). The data are means ± s.e. mean values, expressed as percentages of the controls. Statistical significance (Kruskal-Wallis followed by Mann-Whitney's test): $^{**}P<0.01$, compared with the control value. $^{\#}P<0.05$, comparing data without and with MDL 72222 at the same collection time (Student's t test).

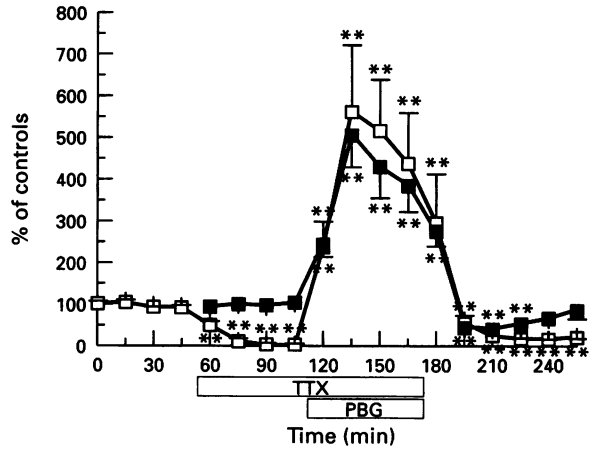


Figure 7 Effect of the perfusion of phenylbiguanide (50 μM) (■, $n=4$) and co-perfusion of phenylbiguanide (50 μM) with tetrodotoxin (1 μM) (□, $n=5$) on the extracellular output of dopamine in the corpus striatum. The data are means ± s.e.mean values, expressed as percentages of the controls. Statistical significance (Kruskal-Wallis followed by Mann-Whitney's test): $^{*}P<0.05$; $^{**}P<0.01$, compared with the control value.

lease of dopamine (Westerink *et al.*, 1987b). Our results show that PBG was able to release dopamine in the presence of TTX, indicating that its effects are not dependent upon neuronal dopaminergic activity. This finding is the first *in vivo* to support the hypothesis that PBG releases dopamine by means of carrier mechanism. Moreover, the decrease in DOPAC output after PBG could be related to a decrease of intraneuronal dopamine. Justice *et al.* (1988) have suggested that there may be three intraterminal pools for dopamine. It is suggested that one pool is nonvesicle-bound. This pool of dopamine is the one into which the uptake carrier places dopamine from the extracellular space. Presumably, this should be the pool from which dopamine is released by carrier-mediated process. Changes in any of the terminal stores may need to be replenished from the newly synthesized dopamine and this circumstance would then lead to a reduction of intraterminal DOPAC. Similarly, the reduction of DOPAC by releasing agents (PBG) would be a consequence of the competition for the newly synthesized store between the release process and metabolism (Zetterström *et al.*, 1988).

Since HVA is, in part, formed from extracellular DOPAC taken by glial cells, the reduction in HVA outflow could be explained as a consequence of the reduction of intraterminal DOPAC. The reduction in DOPAC and HVA outflow is similar in the absence and in the presence of nomifensine. In the latter case, there was no induced increase in the release of dopamine in the presence of PBG, indicating that free intraterminal dopamine was kept under a constant level during PBG perfusion. These results are difficult to explain. In fact, at high PBG concentrations, DOPAC and HVA outflow stays rather low one day after PBG perfusion, but the release of dopamine stays as high as the day of PBG perfusion.

5-HIAA output was not affected by PBG perfusion at any concentration used in the present study. The relatively low density of 5-HT_3 receptor binding reported in the striatum (Kilpatrick *et al.*, 1989; Waeber *et al.*, 1989) could explain these results.

In conclusion, PBG a 5-HT_3 receptor agonist, induced a dose-dependent release of dopamine, which was ameliorated by its co-perfusion with nomifensine and not affected by its co-perfusion with MDL 72222 or TTX. These results suggest that PBG induces a carrier-mediated *in vivo* release of dopamine, which could be independent of the impulse flow.

This research was supported by a grant from DGICYT SAF93-1196, Spain. M.S. is recipient of an Ayuda de la Universidad de Sevilla, Spain.

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(Received April 5, 1995
Revised May 9, 1995
Accepted May 11, 1995)