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Dopamine D_2 activity of *R*-(−)-apomorphine and selected analogs: a microdialysis study

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Abstract

In the present study, *R*-(−)-apomorphine and three of its analogs were studied for their potency in decreasing the release of dopamine in the striatum after subcutaneous administration and for their oral bioavailability using the microdialysis technique in freely moving rats.

The analogs *R*-(−)-*N*-*n*-propylnorapomorphine and *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine displayed a higher potency than *R*-(−)-apomorphine in decreasing the release of dopamine in the striatum. A high dose of *R*-(−)-11-hydroxyaporphine, a dopamine D_2 receptor partial agonist, had a small effect on the release of dopamine in the striatum. The catechols *R*-(−)-*N*-*n*-propylnorapomorphine and *R*-(−)-apomorphine displayed a comparable oral bioavailability (1%), while the mono-hydroxy analog *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine displayed a slightly higher oral bioavailability (3%).

In conclusion, *R*-(−)-*N*-*n*-propylnorapomorphine and *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine did not show a substantial improvement in bioavailability. However, due to the clear difference in their efficacy in decreasing dopamine release, in spite of the similar agonist binding affinities to the dopamine D_2 receptor of the two analogs compared to *R*-(−)-apomorphine, they could be useful alternatives for apomorphine in the treatment of Parkinson's disease.

Keywords: Apomorphine; Dopamine; *N*-propyl analog; Microdialysis; Bioavailability; Striatum

1. Introduction

Parkinson's disease is a progressive neurodegenerative disorder of the basal ganglia, which most often becomes apparent after the age of 55. It is a prototypic hypokinetic disorder, with akinesia, bradykinesia, rigidity and tremor as the most prominent features (Albin et al., 1989). Depression and a general slowing of intellectual processes also occur, but are less well defined. The neurological and psychiatric symptoms usually worsen with time (for review, see Duvoisin, 1987). The neuropathology of Parkinson's disease reveals a striking loss of the dopaminergic neurons of the nigrostriatal pathway (Hornykiewicz, 1966; Bernheimer et al., 1973).

As Parkinson's disease is associated with a loss of dopamine, it is commonly treated with drugs which replace dopamine. Since dopamine itself cannot pass the blood–brain barrier, the most commonly used therapy is levodopa (L-DOPA), a precursor of dopamine. A complication of long-term treatment with L-DOPA, however, is the development of rapid fluctuations in clinical state where the patient switches suddenly between mobility and immobility; this phenomenon is known as the ''on–off effect'' (Marsden and Parkes, 1976, 1977).

An alternative approach to the treatment with L-DOPA is the use of drugs that mimic the action of dopamine. Treatment with dopamine agonists has some advantages over treatment with L-DOPA. Dopamine agonists are effective in patients in the advanced stages of Parkinson's disease unlike L-DOPA, because their action at postsynaptic receptors is unaffected by the lack of dopamine producing nerve cells. Furthermore, there is an increasing interest in the potential of dopamine agonists to provide a neuroprotective effect. Theoretically, such a protective effect might result from (a) a decrease in L-DOPA applica-

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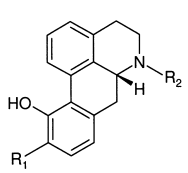
tion, as L-DOPA may cause oxidative stress (Olanow et al., 1998); (b) stimulation of dopamine autoreceptors resulting in decreased dopamine synthesis, release, and turnover, as dopamine metabolism leads to reactive oxygen species (Piercey et al., 1995); (c) direct anti-oxidant effects (Ogawa et al., 1994; Yoshikawa et al., 1994; Nishibayashi et al., 1996).

The dopamine D_1/D_2 receptor agonist *R*-(−)-apomorphine has proven to be very effective in Parkinson's disease. Subcutaneously administered *R*-(−)-apomorphine in combination with L-DOPA rapidly and consistently reverses the ''off'' period motor deficits (Stibe et al., 1988; Frankel et al., 1990; Hughes et al., 1993; Colosimo et al., 1994). Besides its action as a dopamine D_1/D_2 receptor agonist, *R*-(−)-apomorphine can also act as a radical scavenger (Gassen et al., 1996) and, therefore, may have neuroprotective properties. One of the major limitations of the clinical use of *R*-(−)-apomorphine, a catechol–aporphine, however, is its low oral activity (Colpaert et al., 1976; Cotzias et al., 1976; Campbell et al., 1980).

With respect to the low bioavailability of *R*-(−)-apomorphine we initiated a study of three analogs (**2**–**4**) of R-(−)-apomorphine (**1**). The selected analogs all possess affinities for the dopamine D_1 and D_2 receptors comparable to *R*-(−)-apomorphine. It was postulated that the mono-hydroxy compounds would have a higher oral bioavailability, as compared to the catechols, because they are likely to be less sensitive to metabolic degradation. Although a great deal has already been reported on the in vitro and in vivo pharmacology of R-(−)-apomorphine (**1**) and selected analogs (**2**–**4**), no study has been undertaken to examine this series of compounds with respect to their oral bioavailabilities in vivo. We have now examined these compounds with respect to their potencies and relative bioavailabilities, using the microdialysis technique in freely moving rats. By measuring dopamine release in the striatum, information on the degree of dopamine D_2 autoreceptor stimulation can be obtained. Dopamine D_1 receptor stimulation was not investigated in this study. Comparisons were made after subcutaneous s.c. and per oral (p.o.) administration in an attempt to estimate the importance of the first-pass effect for this series of apomorphine analogs (Fig. 1).



1. R_1=OH, R_2=CH_3 R-(–)-apomorphine
2. R_1=H, R_2=CH_3 R-(–)-11-hydroxy-aporphine
3. R_1=OH, R_2=*n*-C_3H_7 R-(–)-N-*n*-propylnorapomorphine
4. R_1=H, R_2=*n*-C_3H_7 R-(–)-11-hydroxy-N-*n*-propylnoraporphine

Fig. 1. Chemical structures of *R*-(−)-apomorphine and selected analogs.

2. Materials and methods

2.1. Animals

Male Wistar rats (from CDL, Groningen, The Netherlands) weighing 280–320 g were used for microdialysis experiments. The rats were housed in plexiglas cages, eight animals in each cage, with free access to water and food. The cages were placed in a room with controlled environmental conditions (21°C; humidity 60%–65%; lights on at 8 AM and off at 8 PM). The animals were housed at least 1 week after arrival prior to surgery. Animal procedures were conducted in accordance with guidelines published in the NIH Guide for the Care and Use of Laboratory Animals and all protocols were approved by the Groningen University Institutional Animal Care and Use Committee.

2.2. Drug treatment

The drugs were dissolved in degassed ultra pure water with approximately 0.5 mg/ml ascorbic acid to prevent oxidation of the compounds and stocked in a concentration of 300 nmol/ml for s.c. administration and 10 μmol/2 ml for oral administration and diluted, if necessary, with degassed ultra pure water before administration. To dissolve *R*-(−)-11-hydroxy-aporphine, a drop of glacial acetic acid was added. Drugs used were *R*-(−)-apomorphine · HCl (**1**), *R*-(−)-11-hydroxyaporphine (**2**), *R*-(−)-*N*-*n*-propylnorapomorphine · HCl (**3**) and *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine · HBr (**4**). *R*-(−)-apomorphine.HCl was purchased from RBI, compounds **3** and **4** were kindly provided by Prof. J.L. Neumeyer (Harvard Medical School, MA), *R*-(−)-11-hydroxy-aporphine (**2**) was synthesized in Groningen.

2.3. Surgery and brain microdialysis

On-line brain microdialysis in freely moving animals has previously been described (Westerink, 1992). In brief, the rats were anesthetized with midazolam (5 mg/kg, s.c.), atropine nitrate (0.1 mg/kg, s.c.), ketamine (50 mg/kg, i.p.) and xylazine (8 mg/kg, i.p.) and 10% lidocaine was locally applied. The rats were then mounted into a stereotaxic frame (Kopf). The incisor bar was placed in position so that the scull was held horizontal. The skull was exposed and burr holes were drilled. A Y-shaped cannula was used for the experiments, with an exposed tip length of 3 mm. The dialysis tube (ID: 0.22 mm; OD: 0.31 mm) was prepared from polyacrylonitrile/sodium methallyl sulfonate copolymer (AN 69, Hospal, Bologna, Italy). The microdialysis membrane was implanted in the striatum. The dura was removed with a sharp needle. Two anchor screws were positioned in different bone plates nearby. The following coordinates were used according to the atlas of Paxinos and Watson (1982): AP + 1.0, LM ± 3.0 relative to bregma, and VD − 6.0 below dura. Before insertion

into the brain the dialysis probe was perfused successively with ultra pure water, methanol, ultra pure water and Ringer solution (1.2 mM Ca^{2+}). The dialysis probe was positioned in the burr hole under stereotaxic guidance. The probe was cemented in this position with phosphatine dental cement. After the surgery the rats received buprenorphine (0.1 mg/kg, i.m.), an analgesic agent. The rats were housed solitary.

The experiments were performed in conscious rats 17–48 h after implantation of the cannula. The striatum was perfused with a Ringer solution (147 mmol/l NaCl, 4 mmol/l KCl, 1.2 mmol/l $CaCl_2$, 1.1 mmol/l $MgCl_2$) at 2 μl/min (CMA/102 microdialysis pump, Sweden). After the experiments, the rats were sacrificed and the brains were removed. After removal, the brains were kept in 4% paraformaldehyde solution until they were sectioned to control the location of the dialysis probe.

Dopamine was quantitated by high-performance liquid chromatography (HPLC) with electrochemical detection with a detection limit of approximately 5 fmol/sample. A HPLC pump (LKB-pharmacia, Sweden) was used in conjugation with an electrochemical detector (Antec, Leiden) working at 625 mV vs. an Ag/AgCl reference electrode. The analytical column was a Supelco Supelcosil LC-18 Column (3 μm particle size). The mobile phase consisted of a mixture of 4.1 g/l sodium acetate (Merck), 85 mg/l octane sulphonic acid (Aldrich), 50 mg/l EDTA (Merck), 8.5% methanol (Labscan) and ultra pure water (pH = 4.1 with glacial acetic acid).

2.4. Data analysis

Data were converted into percentage of basal levels. The basal levels were determined from four consecutive samples (less than 20% variation), and set at 100%. During 180 min after administration of the compound, the dopamine release was measured. This time course was chosen to be able to compare the effects and Areas Under the Curves (AUCs) of the different compounds and routes of administration. The AUC was determined using GraphPad Prism for Windows (GraphPad). To determine the AUC the mean of the first four samples were taken as baseline and then the AUC was calculated from $t = 0$ min to $t = 180$ min. At $t = 180$ min, the program draws an imaginary vertical line and left from this line the AUC is calculated. The experiments were terminated after 180 min to be able to compare the AUCs. The relative oral

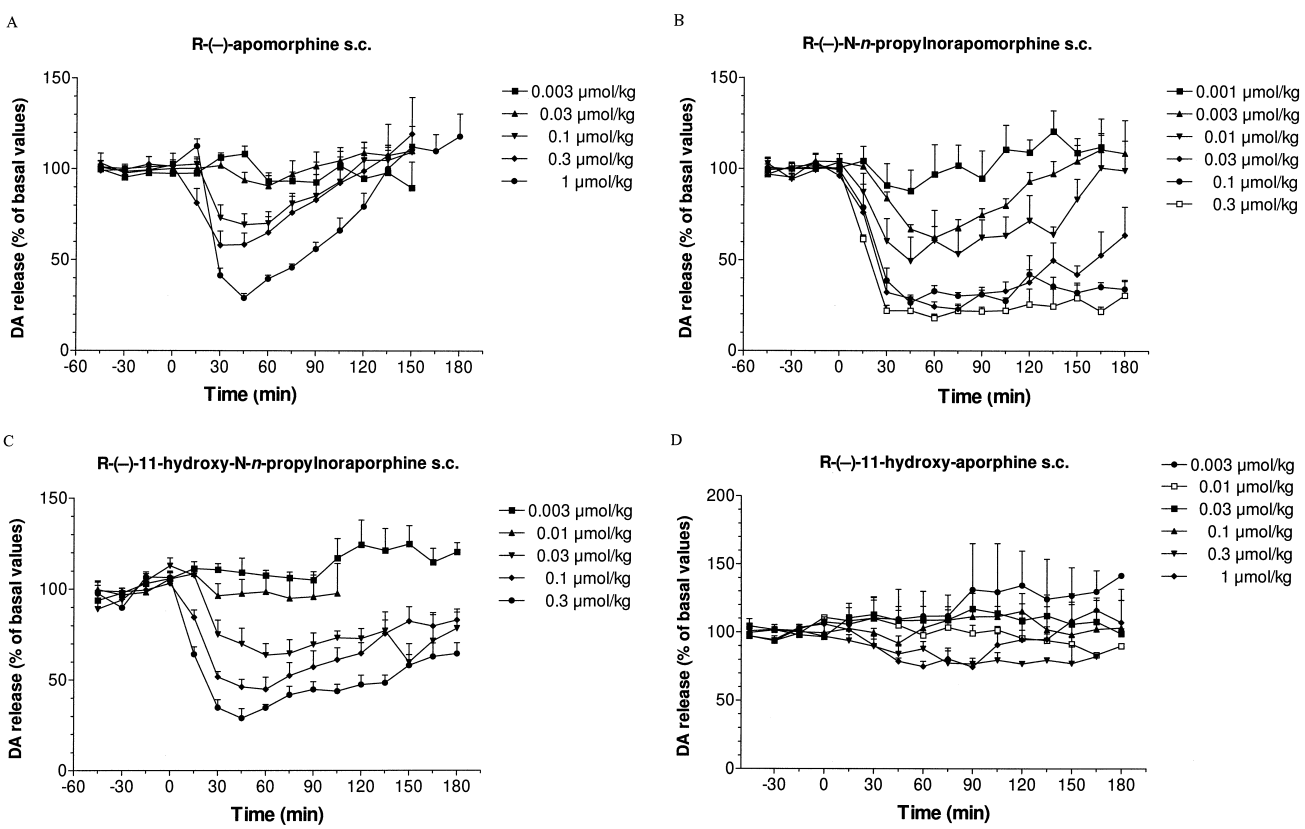


Fig. 2. Effects on striatal dopamine release in freely moving rats after s.c. administration. The results are the mean ± S.E.M. of data obtained from four rats. (A) *R*-(−)-apomorphine (**1**); changes are significant ($p < 0.05$) from $t = 30$ min to $t = 90$ min for 0.1, and 0.3, and from $t = 30$ min to $t = 120$ min for 1 μmol/kg, s.c. (B) *R*-(−)-*N*-*n*-propylnorapomorphine (**3**); changes are significant ($p < 0.05$) from $t = 30$ min to $t = 105$ min for 0.003 and 0.01, from $t = 15$ min to $t = 180$ min for 0.03, 0.1, and 0.3 μmol/kg, s.c. (C) *R*-(−)-11-hydroxy-*N*-*n*-noraporphine (**4**); changes are significant ($p < 0.05$) from $t = 30$ min to $t = 180$ min for 0.03, and 0.1 μmol/kg, s.c., from $t = 15$ min to $t = 180$ min for 0.3 μmol/kg, s.c. (D) *R*-(−)-11-hydroxyaporphine (**2**); changes are significant ($p < 0.05$) from $t = 45$ min to $t = 75$ min for 1 μmol/kg, s.c.

bioavailabilities were determined by comparing the curves after p.o. and s.c. administration. When there was no significant difference between the effects on dopamine release, the s.c. dose was divided by the p.o. dose and multiplied by 100 to give a percentage representing the oral bioavailability. Microdialysis data were compared using one-way analysis of variance (ANOVA) for repeated measurements, followed by Dunnett's Method post-hoc test. A significance level of 0.05 was applied. Statistical analysis of the AUCs was performed by a *t*-test. For comparison with *R*-(−)-apomorphine (**1**) 30 nmol/kg equal variance test failed and then Rank Sum Test followed by Mann–Whitney test was performed.

3. Results

The control dialysate concentrations in the striatum were 11.9 ± 0.7 ($n = 79$) fmol/min. Fig. 2A–D shows that s.c. administration of *R*-(−)-apomorphine (**1**), *R*-(−)-*N*-*n*-propylnorapomorphine (**3**), and *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**), but not *R*-(−)-11-hydroxyaporphine (**2**), induced a dose-dependent decrease in the release of dopamine in the striatum. *R*-(−)-apomorphine (**1**) induced a significant decrease in the release of dopamine in the striatum in a dose-range from 0.1 to 1 μmol/kg, s.c. In a dose-range from 0.003 to 0.3 μmol/kg, s.c., *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) induced a significant decrease in the release of dopamine in the striatum. *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**) induced a significant decrease in the release of dopamine in the striatum in a dose-range from 0.03 to 0.3 μmol/kg, s.c. Although *R*-(−)-11-hydroxyaporphine (**2**) displays affinity for the dopamine D_2 receptor, it only induced a small significant decrease in the release of dopamine in the striatum in a dose of 1 μmol/kg, s.c.

The dose–response relationships of the test compounds are given in Fig. 3. The response of the compounds is given as the AUC. To compare the AUCs, the experiments were slopped after 180 min. The rank order in the potency upon s.c. administration of the compounds is: *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) > *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**) > *R*-(−)-apomorphine (**1**).

The relative oral bioavailabilities of *R*-(−)-apomorphine (**1**) and two of its analogs **3** and **4** can be found from

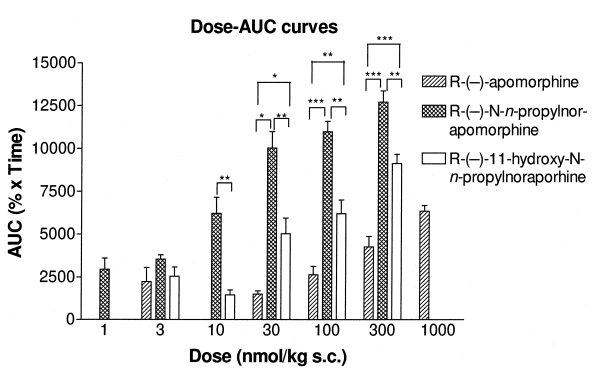


Fig. 3. Comparison of the dose-AUC relationship of *R*-(−)-apomorphine (**1**), *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) and *R*-(−)-11-OH-*N*-*n*-propylnoraporphine (**4**). Data represent mean values ± S.E.M. of four animals. Statistical analysis by *t*-test: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. For comparison with *R*-(−)-apomorphine (**1**), 30 nmol/kg equal variance test failed and then Rank Sum Test followed by Mann–Whitney test was performed.

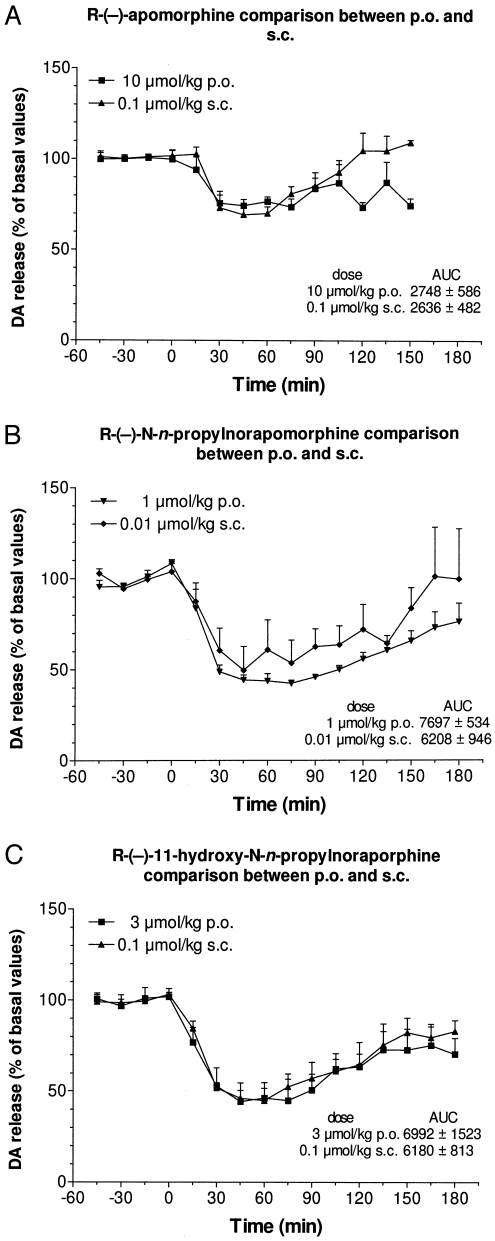


Fig. 4. Effects on striatal dopamine release in freely moving rats after s.c. and p.o. administration. The results are the mean ± S.E.M. of data obtained from four rats. (A) *R*-(−)-apomorphine (**1**); changes are significant ($p < 0.05$) from $t = 30$ min to $t = 90$ min for 0.1 μmol/kg, s.c. and 10 μmol/kg, p.o. (B) *R*-(−)-*N*-*n*-propylnorapomorphine (**3**); changes are significant ($p < 0.05$) from $t = 30$ min to $t = 105$ min for 0.01 μmol/kg, s.c. and for $t = 15$ min to $t = 180$ min for and 1 μmol/kg, p.o. (C) *R*-(−)-11-hydroxy-*N*-*n*-noraporphine (**4**); changes are significant ($p < 0.05$) from $t = 30$ min to $t = 180$ min for 0.1 μmol/kg, s.c., from $t = 15$ min to $t = 180$ min for 3 μmol/kg, p.o.

Fig. 4A–C. The relative oral bioavailability was determined by comparing the curves and the AUC after s.c. and oral administration. When the AUCs were not significantly different, the relative oral bioavailability was determined by dividing the s.c. dose by the p.o. dose and multiplied by 100. It was known that *R*-(−)-apomorphine (**1**) possessed a low oral bioavailability. It was expected that the oral bioavailability of the three compounds would be between 1% and 10%. Based on this assumption the oral doses were chosen. With this method, both the catechols *R*-(−)-apomorphine (**1**) and *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) possess a relative oral bioavailability of about 1%. The mono-hydroxy compound *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**) possesses a relative oral bioavailability of about 3%.

When the courses of the curves after s.c. administration of compounds **1**, **3** and **4**, respectively, are compared it can be seen that the duration of action of the *N*-propyl analogs is longer than that of *R*-(−)-apomorphine (**1**).

Compound **2** does not induce an effect on the release of dopamine from the striatum (Fig. 2D). The binding data together with literature data suggest that this compound is a partial dopamine D_2 receptor agonist and a dopamine D_1 receptor antagonist (Schaus et al., 1990). Therefore, the present pharmacodynamic method was not suitable to determine the relative oral bioavailability.

4. Discussion

R-(−)-apomorphine (**1**) is a catechol and is known to have a low oral bioavailability (Neumeyer and Baldessarini, 1997). However, the drug is very useful in the treatment of Parkinson's disease when L-DOPA treatment gives ''on–off'' fluctuations (Stibe et al., 1988). An analog which also displays dopamine D_1 and D_2 receptor agonistic properties, but possessing a higher oral bioavailability, would be beneficial as an alternative treatment in Parkinson's disease. The analogs tested (*R*-(−)-11-hydroxyaporphine (**2**), *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) and *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**)) possess affinities for the dopamine D_1 and D_2 receptors comparable to *R*-(−)-apomorphine (**1**) (Table 1). In our experiments, we monitored the dopamine D_2 receptor agonistic properties of the compounds, as the release of dopamine is under the control of dopamine D_2 autoreceptors (Westerink et al., 1990).

Fig. 2A–C show that compounds **1**, **3** and **4** act as dopamine D_2 receptor agonists, because they all induce a decrease in the release of dopamine in the striatum. *R*-(−)-11-hydroxyaporphine (**2**) (Fig. 2D) induces, in a dose of 1 μmol/kg, a small significant decrease in the release of dopamine in the striatum. This lack of biochemical activity of compound **2** was not expected from a structure-activity point of view. However, Schaus et al. (1990) already published that *R*-(−)-11-hydroxyaporphine (**2**) acts as a partial agonist at the dopamine D_2 receptor. This would explain our findings that this compound has a very weak effect on the dopamine D_2 autoreceptor.

The dose–AUC relationships upon s.c. administration (Fig. 3) clearly show that the *N*-*n*-propyl analogs (**3**,**4**) are more efficacious in the microdialysis experiments than the *N*-methyl analog (*R*-(−)-apomorphine (**1**)). An explanation could be the presence of a propyl moiety on the nitrogen for *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) because a propyl grows has a better fit into the receptor than a methyl group. This, however, should have been shown in differences in binding affinities, which are not observed. Although there is a clear distinction in efficiency in the microdialysis experiments between the three compounds, this difference cannot be explained by the affinities for the dopamine D_2 receptor (Table 1). The relevant dopamine D_2 receptor agonist binding is comparable for the three compounds.

Fig. 4A and B shows that both the catechol-containing aporphines (*R*-(−)-apomorphine (**1**) and *R*-(−)-*N*-*n*-propylnorapomorphine (**3**)) possess a relative oral bioavailability of about 1%. The greater s.c. potency of *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) over *R*-(−)-apomorphine (**1**)

Table 1
Affinities of *R*-(−)-apomorphine (**1**) and its selected analogs (**2**–**4**)
Affinity of *R*-(−)-apomorphine (**1**) and its selected analogs (**2**–**4**) as measured by their ability to displace in vitro [^{3}H]SCH23390 (D_1-antagonist), [^{3}H]spiperone (D_2-antagonist), and [^{3}H]ADTN (D_2-agonist) from membrane preparations of rat brain corpus striatum tissue in order to measure the affinity for dopamine D_1 and D_2 receptors, respectively.

Compound	K_i (nM)		
	[^{3}H]SCH23390 (D_1)	[^{3}H]spiperone (D_2-antagonist)	[^{3}H]ADTN (D_2-agonist)
R-(−)-apomorphine (**1**)[a]	240	11.1	3.7
R-(−)-11-hydroxyaporphine (**2**)[b]	*107*[c]	*58*[c]	–
R-(−)-*N*-*n*-propylnor-apomorphine (**3**)[a]	340	0.8	1.5
R-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**)[d]	434	0.9	5.3

[a] Values are taken from (Gao et al., 1990).
[b] Values are taken from (Schaus et al., 1990).
[c] IC50 in nM.
[d] Values are taken from (Neumeyer et al., 1991).

is not likely to be the result from different rates of metabolism in the periphery because the main route of metabolism for both compounds is glucuronidation of the catechol moiety (Schoenfeld et al., 1975). The greater potency of the mono-hydroxy analog *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**) (Fig. 4) could possibly be explained from differences in metabolism, *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**) possesses a relative oral bioavailability of 3%. Although this represents an increase, it is still not an optimal oral bioavailability for a therapeutic agent. The improvement of the relative oral bioavailability of the mono-hydroxy analog (**4**) may be explained from the fact that a mono-hydroxy analog is less sensitive to metabolic degradation than a catechol moiety (Campbell et al., 1990). Beside glucuronidation, the catechol moiety is also sensitive to oxidative degradation, as well as to degradation by catechol-*O*-methyl transferase (COMT), which will predominantly result in 10-methoxy-11-hydroxyaporphine, an inactive compound (Arana et al., 1984; Cannon and Qijie, 1991). The catechol moiety is clearly not necessary for high affinity at the dopamine D_2 receptors. The presence of a free 11-hydroxy moiety is enough to confer dopamine D_2 receptor agonist-like activity, similar to that of 10,11-dihydroxyaporphines (Campbell et al., 1990).

An explanation could be differences in intrinsic efficacy and differences in the ability to pass the blood–brain barrier. For *R*-(−)-*N*-*n*-propylnorapomorphine (**3**), this difference in ability to pass the blood–brain barrier compared to *R*-(−)-apomorphine has previously been published (Costall et al., 1975; Schoenfeld et al., 1975; Kelly et al., 1976).

Beside comparable effects on the release of dopamine in the striatum, *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) and *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**) could also possess the same neuroprotective effects as *R*-(−)-apomorphine. This neuroprotective effect resides in the phenolic moiety, which can act as a radical scavenger (Ogawa et al., 1994; Yoshikawa et al., 1994; Nishibayashi et al., 1996). Both compounds possess this moiety.

Based on our results, *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) and *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**) could be good targets for treatment of Parkinson's disease. Although their oral bioavailabilities are low good, their greater efficacy results in the possibility of administering lower doses. *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) has proven to be a useful adjunct in the long-term management of patients with unsatisfactory response to L-DOPA and produced a significant therapeutic benefit at doses much lower than the dose at which side effects occur (Papavasiliou et al., 1978).

In conclusion, this microdialysis study shows that *R*-(−)-*N*-*n*-propylnorapomorphine (**3**) and *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**4**) are more potent than *R*-(−)-apomorphine (**1**) in inhibiting dopamine release in the striatum. This difference in potency on the presynaptic receptors resembles the difference in potency of these analogs on supersensitive postsynaptic receptors as described by Kelly et al. (1976).

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