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A study of tolerance to apomorphine

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1 The present study was designed to investigate tolerance to several pharmacological effects of apomorphine.

2 Changes in blood pressure, heart rate, plasma noradrenaline levels, rectal temperature, respiratory rate and retching plus vomiting were compared after administration of apomorphine (200 $\mu g\ kg^{-1}$, i.v. as a bolus) or saline at different time intervals (30, 120 and 720 min) in four groups of chloralose-anaesthetized dogs.

3 The first administration of apomorphine induced a significant decrease in blood pressure and rectal temperature, a marked rise in heart rate with no change in noradrenaline plasma levels or respiratory rate. Emesis occurred in 71% of the animals.

4 A second administration of apomorphine 30 min later failed to modify blood pressure or heart rate. In contrast, the magnitude of apomorphine-induced changes in blood pressure and heart rate was similar to that observed after the first administration when apomorphine was given 120 or 720 min later.

5 The apomorphine-induced decrease in rectal temperature evoked by a second dose of apomorphine was less marked when given 30 and 120 min after the first dose and unchanged when given 720 min later.

6 The number of animals exhibiting retching and vomiting was lower when apomorphine was reinjected after 30 min than when the time between two successive injections of apomorphine was 120 or 720 min.

7 These results show that tolerance to apomorphine involves its cardiovascular, hypothermic and emetic effects. The time course of tolerance to repeated injections of apomorphine is longer for its hypothermic than for its hypotensive or emetic effects. This suggests a tissue-specific regulation of D_2 dopamine receptors to repeated injections of apomorphine.

Keywords: Apomorphine; tolerance; blood pressure; temperature; vomiting

Introduction

Apomorphine is the most potent dopamine receptor agonist now available for human subjects. It is used in preclinical (Colpaert *et al.*, 1976) and clinical (Lals, 1988) pharmacology as a reference drug. It acts as a non selective D_1 and D_2 dopamine receptor agonist (Neumeyer *et al.*, 1981). It is now widely used in clinical practice by the subcutaneous route in the treatment of refractory 'on-off' oscillations in patients with Parkinson's disease treated with levodopa (Lees, 1993; Montastruc *et al.*, 1993; Nicolle *et al.*, 1993).

Several experimental and clinical studies have discussed the occurrence of behavioural tolerance to repeated apomorphine administration. However, the results are conflicting. For example, in rats with unilateral 6-hydroxydopamine (6-OHDA) lesions, successive apomorphine injections separated by 2 h intervals were accompanied by a significant reduction in turning behaviour, whereas one daily dose resulted in increased rotational response (Castro *et al.*, 1985). More recently, Gancher *et al.* (1995a) suggested that tolerance to apomorphine is duration- and dose-dependent in rats with unilateral 6-OHDA lesions. In Parkinsonian monkeys, Luquin *et al.* (1993) found that behavioural hyposensitivity to repeated administration of apomorphine occurs preferentially when near-threshold doses are given at short intervals (30 min). This apomorphine-induced tolerance was also described in Parkinsonian patients by Grandas & Obeso (1989) whereas Hughes *et al.* (1991) did not find any significant change in the duration of motor responses to sequential subcutaneous apomorphine in a group of 15 patients with Parkinson's disease and levodopa-induced motor fluctuations. Grandas *et al.* (1992) demonstrated that the duration of 'on' responses to apomorphine was reduced by 40% after a 2 h interval but remained unchanged after a 4 h interval. Recently, Gancher *et al.* (1995b), investigating six patients with Parkinson's disease treated for 3 months with subcutaneous infusions of apomorphine during waking hours concluded that there was a lack of tolerance to this drug.

Beside behavioural and motor effects, apomorphine is known to induce several other pharmacological effects such as arterial hypotension (Montastruc *et al.*, 1985; Rascol & Montastruc, 1986), nausea, vomiting (Corsini *et al.*, 1981) and hypothermia (Colpaert *et al.*, 1976). As far as we know, the tolerance to these various pharmacological effects of apomorphine has never been investigated. Thus, it was the aim of the present study to investigate the pattern of these responses to repeated injections of apomorphine at different intervals of time.

Methods

General procedure

Beagle dogs of either sex (10-15 kg body weight) were used. After an overnight fast, they were anaesthetized with α-chloralose (80 mg kg^{-1}, intravenous, i.v.) and intubated with a cuffed endotracheal tube to allow spontaneous ventilation. The mean systemic arterial blood pressure was measured with a Statham P23 Id pressure transducer inserted into the left femoral artery and displayed on a Honeywell Bull recorder. Heart rate was obtained with a heart period (pulse interval) meter triggered by blood pressure intervals.

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Experimental protocol

Four groups of dogs were used. The first group ($n=8$, experiment 1) received a first i.v. injection of apomorphine hydrochloride (200 $\mu g\ kg^{-1}$) at time 0 and a second, (200 $\mu g\ kg^{-1}$, i.v.) 30 min later. Apomorphine was administered as a bolus. The dose was chosen according to the results of previous experiments from our group in order to induce significant changes in blood pressure. Lower doses (50 or 100 $\mu g\ kg^{-1}$) did not induce a significant and constant decrease of blood pressure (Montastruc *et al.*, 1985; 1992). The second group ($n=8$, experiment 2) received two successive injections of apomorphine (200 $\mu g\ kg^{-1}$ i.v.) at 0 and 120 min whereas the third group ($n=8$, experiment 3) was treated by the same dose of apomorphine at time 0 and 720 min. The fourth group ($n=8$, experiment 4) was used as control and received i.v. saline as a sham injection at 0, 30, 120 and 720 min. During the whole experiment, a constant level of anaesthesia was maintained by an injection of 15 to 20 mg kg^{-1} of chloralose each hour. The animals were placed under an insulating cover and four hot water bottles (full of water at 40°C) were placed near their flanks. The hot water bottles were changed every hour. This protocol, which was applied to the four groups of animals, allows body temperature to be maintained constant at around 38°C during the whole experiment in the control group (experiment 4). Under these conditions, the mean blood pressure and heart rate were measured at 0, 1, 2, 5, 10, 15, 20, 25 and 30 min after apomorphine injection. The respiratory rate was measured with a Paul Bert pneumograph at 0 min and every 5 min during the 30 min following the injection of apomorphine. Rectal temperature was measured 0, 1, 2, 5 min and every 5 min during the first 30 min after apomorphine with an automatic electrical thermometer (HP 5316 Philips). The number of vomitings and retchings elicited by apomorphine was counted by a 'blind' uninformed observer (Watson *et al.*,1995). When vomiting or retching occurred during measurement of blood pressure or heart rate values, a lapse of at least 60 s after the end of the last vomiting or retching was allowed until the cardiovascular parameters returned to preretching values.

Blood sampling and catecholamine assays

At time 0 and 5 min after apomorphine injection, arterial blood was taken from the catheter previously introduced into the abdominal aorta to prevent any stress. It was collected on lithium heparin with sodium metabisulphite (10 $\mu mol\ l^{-1}$), centrifuged at 4000 r.p.m. for 15 min at 4°C and the plasma was stored at −80°C. Catecholamines were isolated selectively from the sample at 0°C, in darkness, by adsorption on activated alumina, then eluted with 0.1 $mol\ l^{-1}$ acetic acid. Dihydroxybenzylamine was used as internal standard. Noradrenaline was assayed by a Waters high-performance liquid chromatography apparatus using electrochemical detection: the working electrode potential was set at 0.65 V against a Ag/AgCl reference electrode. Catecholamines were separated on a C18 column (3.9 × 150 mm) at a constant flow rate of 1 ml min^{-1}. The electrochemical detector response was linear for concentrations ranging from 60 pmol l^{-1} to 600 nmol l^{-1}. In these conditions, the detection limit is 60 pmol l^{-1} to 600 nmol l^{-1} (Poncet *et al.*, 1991; Tavernier *et al.*, 1993).

Statistical analysis

Results (expressed as mean values ± s.e.mean) were analysed by ANOVA followed by a Bonferroni test. The non-parametric Fisher's test was used for the comparisons of vomiting in the different groups. The level of significance was $P<0.05$.

Drugs used

α-Chloralose (Sigma Laboratories) was dissolved in isotonic saline (0.9% NaCl). Apomorphine hydrochloride was used from sterile commercial ampoules (Apokinon, Aguettant Laboratories, Lyon, France).

Results

Effects of the first injection of apomorphine

Only the results with apomorphine will be presented since in experiment 4 (not shown) using saline as a vehicle, we failed to show any significant change in blood pressure, heart and respiratory rates, plasma noradrenaline levels or rectal temperature. No vomiting occurred after saline.

There was no significant difference between the basal values of the different parameters (blood pressure, heart rate, respiratory rate, rectal temperature and plasma noradrenaline levels) in the three different groups (Table 1).

Figure 1 shows the effects of a first acute injection of apomorphine. Apomorphine induced both a marked decrease in mean blood pressure and an increase in heart rate which remained statistically significant until the 30th min. The peak effect was observed at the 5th min. The respiratory rate did not change whereas the rectal temperature significantly decreased. Vomiting occurred in 71% of the animals (17/24) (Table 2). Plasma noradrenaline values did not change (150 ± 20 pg ml^{-1} at time 0 versus 158 ± 30 pg ml^{-1} 5 min after apomorphine).

Effects of the second injection of apomorphine

Since there was no significant change in respiratory rate or plasma noradrenaline levels after apomorphine, we present

Table 1 Resting (pre-apomorphine) values of mean blood pressure (BP in mmHg), heart rate (HR in beats min^{-1}) and rectal temperature (in °C) in the three groups of dogs receiving apomorphine at time 0 and after a 30 (experiment 1, $n=8$), 120 (experiment 2, $n=8$) and 720 (experiment 3, $n=8$) min interval

	Experiment 1	*Experiment 2*	*Experiment 3*
BP (mmHg)			
Before the first injection	112 ± 4	117 ± 5	117 ± 7
Before the second injection	99 ± 4*#	135 ± 8	134 ± 6
HR (beats min^{-1})			
Before the first injection	98 ± 7	94 ± 6	99 ± 5
Before the second injection	124 ± 6	112 ± 9	88 ± 8*#
Rectal temperature (°C)			
Before the first injection	38.0 ± 0.1	38.0 ± 0.2	37.7 ± 0.2
Before the second injection	37.2 ± 0.1*	36.6 ± 0.3*	37.2 ± 0.6*

*$P<0.05$ when compared with the value before the first injection. #$P<0.05$ when compared with the other values before the second injection. Values are mean ± s.e.mean.

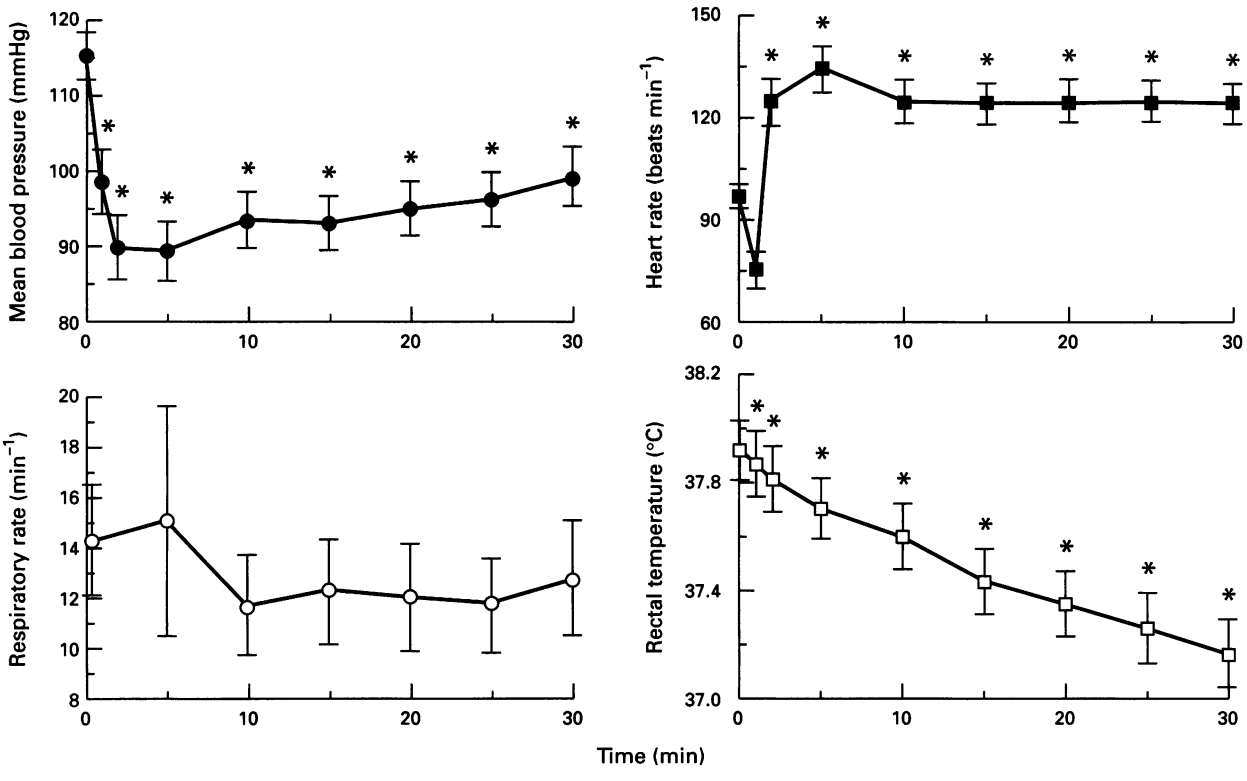

Figure 1 Effects of a single injection of apomorphine (200 μg kg^{-1}, i.v. as a bolus) in chloralose-anaesthetized dogs on mean blood pressure (mmHg), heart rate (beats min^{-1}), respiratory rate (min^{-1}) and rectal temperature (°C). Apomorphine was injected at time 0. $n=24$. Mean values ± s.e.mean are shown. *$P<0.05$ versus values at time 0.

Table 2 Comparison of occurrence of vomitings and retchings elicited by apomorphine according to the different time intervals between the two injections

Time interval	*First injection*	*Second injection*
30 min	7/8	2/8*
120 min	5/8	5/8
720 min	5/8	5/8

The table shows the number of dogs which vomited versus the number that did not. *$P<0.05$ when compared with the first injection using Fisher's test.

only the results concerning tolerance to the cardiovascular, hypothermic and emetic effects of apomorphine.

Figure 2 compares the changes in blood pressure and heart rate observed 5 min after the two injections. This time was chosen because the maximum cardiovascular effect of apomorphine was observed 5 min after apomorphine (Figure 1). In experiment 1, the second injection of apomorphine failed to change blood pressure significantly when compared with the basal value. In contrast, the magnitude of the decrease in blood pressure was similar after the first and the second injection in experiments 2 (120 min interval) and 3 (720 min interval) (Figure 2). Similar results were obtained for heart rate. The second injection of apomorphine did not induce changes in heart rate in experiment 1. In contrast, when the injections were separated by a 120 or 720 min interval, apomorphine induced an increase like that observed after the first injection.

Figure 3 indicates that apomorphine induced a decrease in rectal temperature in the three experiments. However, the magnitude of the decrease was lower after the second injection in experiment 1 (30 min interval) and 2 (120 min interval) but not in experiment 3 (720 min interval).

Vomiting occurred in 71% of the animals after the first administration, in 25% after 30 min (experiment 1) ($P<0.05$ when compared with the first injection), and in 62.5% after 120 (experiment 2) or 720 min (experiment 3) (not significant when compared with the first injection) (Table 2).

Discussion

Besides its central behavioral actions (stereotyped behaviour, change in motor activity, agression, sexual behaviour), apomorphine is known to induce several other pharmacological effects: vomiting, hypothermia, arterial hypotension, increase in growth hormone serum levels, decrease in plasma prolactin concentration, etc. (Colpaert *et al.*, 1976). The possibility of behavioural tolerance to repeated apomorphine administration has been investigated previously (Castro *et al.*, 1985; Grandas & Obeso, 1989; Hughes *et al.*, 1991; Grandas *et al.*, 1992; Gancher *et al.*, 1995a, b). In contrast, the tolerance to other pharmacological effects has not been widely studied. The present experiments were designed to investigate the putative tolerance to the other well characterized pharmacological actions of apomorphine. Apomorphine was used at only one dosage known to induce marked and reproducible arterial hypotension (Montastruc *et al.*, 1985; 1994) in dogs. Although conflicting results have been obtained, several studies have concluded that behavioural tolerance to apomorphine is duration- and dose-dependent (Grandas *et al.*, 1992; Gancher *et al.*, 1995a). Under our experimental conditions, apomorphine induced a decrease in blood pressure, an increase in heart rate, hypothermia and vomiting with no change in respiratory rate or plasma noradrenaline levels.

Several authors have investigated the mechanisms of apomorphine-induced arterial hypotension in animals and man. Although some authors have found arguments for a central site of action of apomorphine (Lahlou *et al.*, 1990), it is usually thought that apomorphine reduces blood pressure because of

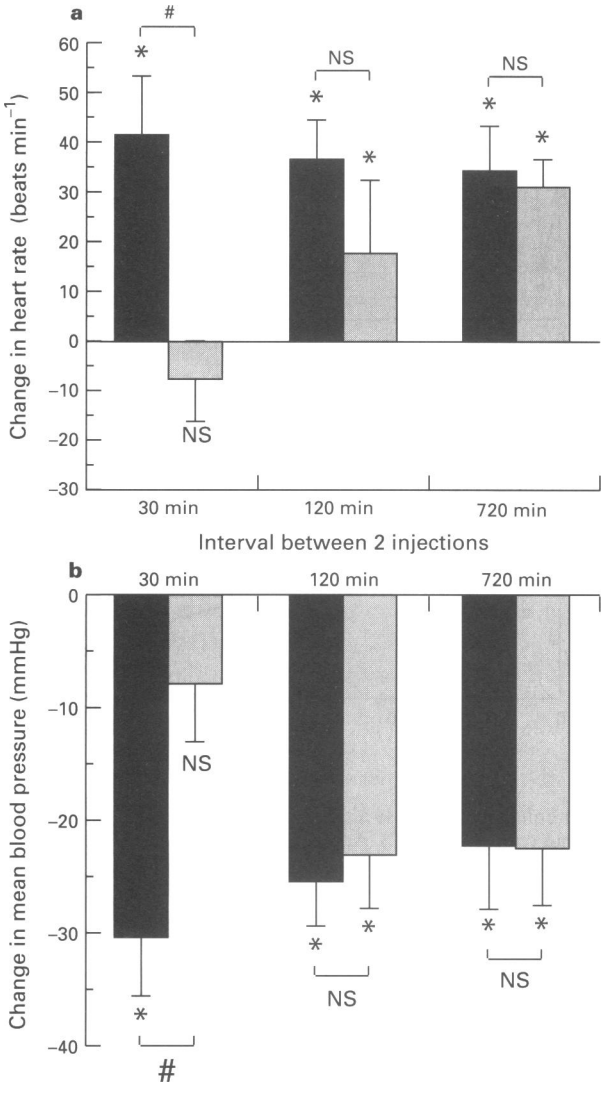

Figure 2 Effects of two successive injections of apomorphine ($200\,\mu g\,kg^{-1}$, i.v. as a bolus) on heart rate (in a, beats min^{-1}) and mean blood pressure (in b, mmHg) in chloralose-anaesthetized dogs. The figure shows the maximal changes observed at the 5th min versus time 0 min. Solid columns represent the effects of the first injection and the stippled columns the effects of the second injection performed after 30 (experiment 1, $n=8$), 120 (experiment 2, $n=8$) or 720 (experiment 3, $n=8$) min intervals. Mean values ± s.e.mean are shown. $^{*}P<0.05$ versus basal resting value. $^{\#}P<0.05$ between the two successive injections (time 0 versus 30 min).

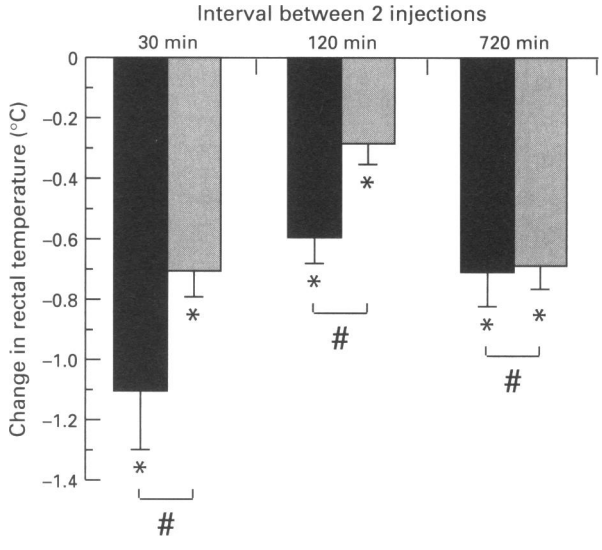

Figure 3 Effects of two successive injections of apomorphine ($200\,\mu g\,kg^{-1}$, i.v. as a bolus) on rectal temperature (°C) in chloralose-anaesthetized dogs. The figure shows the changes recorded at the 30th min versus time 0 min. Solid columns represent the effect of the first injection and the stippled columns the effects of the second injection performed after 30 (experiment 1, $n=8$), 120 (experiment 2, $n=8$) or 720 (experiment 3, $n=8$) min intervals. Mean values ± s.e.mean are shown. $^{*}P<0.05$ versus basal resting value. $^{\#}P<0.05$ between the two successive injections (time 0 versus 30 min).

its ability to activate peripheral presynaptic D_2 dopamine receptors leading to a decrease in noradrenaline release from the sympathetic nerve endings (Montastruc *et al.*, 1985; Willems *et al.*, 1985; Rascol & Montastruc, 1986). The increase in heart rate is mainly of baroreflex origin (Montastruc *et al.*, 1985). In the present study, because of the experimental conditions (experiments performed in anaesthetized animals over several hours), basal resting values of cardiovascular parameters were not always similar. However, despite these differences, we clearly found that the second injection of apomorphine performed after a 30 min interval did not change the blood pressure or heart rate. This observation cannot be explained by a too low level of resting blood pressure since in other experiments (not shown) we found that, at this level (99 mmHg), blood pressure can be decreased by several pharmacological manipulations. Thus, we can conclude that there is a tolerance to the cardiovascular effects of apomorphine after a 30 (but not a 120 or 720) min interval between two successive injections. The mechanism of apomorphine-induced tolerance is not clear. It could involve baroreflex resetting or desensitization of presynaptic dopamine receptors located on sympathetic nerve endings. Using ropinirole, another selective D_2 dopamine receptor agonist, Parker *et al.* (1994) discussed another mechanism for the apparent tolerance to the cardiovascular effects: they suggested an increased sympathetic tone to resistance vessels. We cannot confirm this hypothesis since in the present study, we failed to find any evidence for change in plasma noradrenaline levels.

It is clearly demonstrated that apomorphine induces a marked hypothermic effect in several species (Colpaert *et al.*, 1976). The drug operates by stimulating dopamine receptors located in an area of the anterior hypothalamus, the nucleus preopticus medialis through the activation of the D_2 and/or D_4 subtype (Costentin *et al.*, 1990). We found a significant decrease in the hypothermic response to apomorphine after a single administration of apomorphine 30 or 120 min beforehand. Costentin *et al.* (1975) found that tolerance to the hypothermic effect of apomorphine occurs 2 h after a single dose of apomorphine in mice. They suggested that dopamine receptors controlling thermoregulation are easily desensitized by a sustained stimulation but not hypersensitized by a semichronic blockade. This contrasts to dopamine receptors mediating climbing behaviour which are characterized by their ability to become hypersensitized and their inability to exhibit desensitization (Costentin *et al.*, 1975).

It is well accepted that apomorphine-induced vomiting is mediated by activation of dopamine D_2 receptors because this effect is abolished by pretreatment with haloperidol or domperidone (Rautsen & Ochs, 1973) but not with naloxone (Montastruc *et al.*, 1994). Apomorphine mainly acts on the so-called chemoreceptor trigger zone, a chemosensitive region where dopamine receptors have been described (Mitchelson, 1992). The present study suggests a rapid desensitization of these D_2 dopamine receptors which does not recover within a 30 min interval.

In conclusion, the present study shows that tolerance to repeated injections of apomorphine involves its cardiovascular (decrease in blood pressure and increase in heart rate), hypothermic and emetic effects. Pharmacokinetic factors are an

unlikely explanation for our findings since the available pharmacokinetic studies with apomorphine show that within-subject variation in absorption after repeated subcutaneous administration is low (Gancher *et al.*, 1989; Grandas & Obeso, 1989; Montastruc *et al.*, 1991). Although the present experiments were not designed to investigate cellular mechanisms, one could hypothesize (as suggested by Costentin *et al.*, 1975; 1990) that tolerance to repeated injections of apomorphine involves D_2 dopamine receptor desensitization. Our work also suggests a different time course of desensitization of D_2 dopamine receptors involved in these mechanisms since tolerance to cardiovascular and emetic effects of apomorphine disappeared after 2 h and persisted for hypothermic effects for at least 2 h. Thus, as previously reported for α_2- (Estan *et al.*, 1990; Portillo *et al.*, 1991) and β_3-(Chaudry & Granneman, 1994) adrenoceptors, the present study suggests a tissue-specific regulation of D_2 dopamine receptors to repeated injection of apomorphine. Further studies are needed to investigate the mechanism of this tissue-specific regulation which could involve different D_2 dopamine receptor subtypes or different receptor-coupling mechanisms (Andersen *et al.*, 1990; Caccavelli *et al.*, 1992).

Finally, Parker *et al.* (1994) described tolerance to the peripheral (arterial hypotension) but not central (hypolocomotor effects) effects of ropinirole, a selective D_2 dopamine agonist, in rats. Our results suggest that different centrally-mediated effects show different degrees of tolerance to apomorphine.

Since apomorphine is now widely used in the treatment of Parkinsonian patients (Lees, 1993; Montastruc *et al.*, 1993), the present data could have important clinical consequences. Tolerance to the cardiovascular effects of two other D_2 dopamine agonists has been previously described in man (Teychenne *et al.*, 1980). In such patients treated with apomorphine by several daily subcutaneous injections, persistent hypotension, vomiting or hypothermia would lead to a reduction in patient tolerance and compliance.

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