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Effects of GBR 12909 on locomotor activity and dopamine turnover in mice: comparison with apomorphine

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Abstract

The effects of GBR 12909 1-[2-[bis(4-fluorophenyl)methoxy]-ethyl]-4-[3-phenylpropyl]piperazine, a very potent and selective dopamine uptake inhibitor, and apomorphine, a dopamine receptor agonist, alone and in combination were investigated on locomotor activity and dopamine turnover in discrete brain regions of mice. The levels of dopamine and its metabolites were examined 40 min after the administration of GBR 12909 and/or apomorphine, when the effects of the drugs on locomotor activity were approximately at a peak. GBR 12909 (10 mg/kg i.p.) reversed a low dose of apomorphine (0.05 mg/kg s.c.)-induced suppression in locomotor activity and significantly increased this activity. Despite the dramatic change in the behavior, GBR 12909 did not influence the decrease in 3,4-dihydroxyphenylacetic acid (DOPAC)/dopamine ratio (which is one of the indications of transmitter turnover) induced by a low dose of apomorphine in the nucleus accumbens and striatum. In contrast, GBR 12909 did not enhance the high-dose apomorphine (2 mg/kg s.c.)-induced hyperlocomotion, and did not modify the larger decrease in dopamine turnover produced by the high dose of apomorphine in the frontal cortex, nucleus accumbens and striatum. This suggests that postsynaptic dopamine receptors may reach maximum stimulation at a high dose of apomorphine. These results indicate that a behavioral change induced via stimulation of postsynaptic dopamine receptors does not necessarily lead to an alteration in dopamine turnover.

Keywords: Dopamine uptake inhibitor; Dopamine receptor agonist; Dopamine, endogenous; Frontal cortex; Nucleus accumbens; Striatum

1. Introduction

GBR 12909 1-[2-[bis(4-fluorophenyl)methoxy]-ethyl]-4-[3-phenylpropyl]piperazine dihydrochloride is a very potent and selective dopamine uptake inhibitor which specifically binds to the dopamine uptake site and does not stimulate the release of dopamine (Andersen, 1987, 1989; Heikkila and Manzino, 1984; Soares-da-Silva and Garrett, 1990). Dopamine uptake blockers can elevate synaptic levels of endogenous dopamine by inhibiting the re-uptake of released dopamine into presynaptic terminals. Therefore, it is hypothesized that inhibitors of dopamine uptake reduce dopamine metabolism and turnover in vivo owing to the inhibition of activity of dopamine neurons resulting from activation of transsynaptic feedback pathways. However, it has been shown that GBR 12909 and amfonelic acid, another selective dopamine uptake inhibitor (which has minimal dopamine-releasing effects), have no effects on dopamine metabolism in the striatum of rats (Westerink et al., 1987) and that neither mazindol, another dopamine uptake inhibitor, nor amfonelic acid changes the levels of 3,4-dihydroxyphenylacetic acid (DOPAC) in whole brain of rats (Fuller and Snoddy, 1979). In contrast, it has been reported that amfonelic acid significantly increases dopamine metabolism in the striatum of rats (Shore, 1976). The reason for the discrepancy between the hypothesis and these findings is unknown at present.

The purpose of this study was to clarify the effects of GBR 12909 on locomotor activity and dopamine turnover in the frontal cortex, nucleus accumbens and

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striatum, and to compare these effects with those of apomorphine, a dopamine receptor agonist. Additionally, we examined whether GBR 12909 would influence apomorphine-induced locomotor activity or dopamine metabolic change. It is well known that low doses of apomorphine decrease locomotor activity in rodents and this decreasing effect is attributed to activation of dopamine autoreceptors. Stimulation of somatodendritic autoreceptors decreases impulse flow and therefore reduces levels of dopamine metabolites and dopamine turnover. In contrast, higher doses of apomorphine increase locomotor activity through postsynaptic dopamine receptor stimulation. This increased postsynaptic receptor stimulation causes a reduction in dopaminergic activity via activation of negative neuronal feedback loops and a consequent larger decrease in dopamine turnover (Cooper et al., 1991a; Wolf and Roth, 1987).

2. Materials and methods

2.1. Animals

Adult male ddY mice (Kuroda Junkei Doubutsu, Japan), weighing 34–48 g, were used. The animals were housed with free access to food and water in an air-conditioned room with a temperature of 22–24°C and humidity of 45–55% and maintained under a constant 12-h light-dark cycle (lights on at 07:00 h). All behavioral experiments were carried out between 10:00 and 18:00 h.

2.2. Locomotor activity

Locomotor activity was measured with four circular activity cages (49 cm diameter × 26.5 cm high). Each cage was equipped with three photocell sensor units mounted on the outer wall at equal distances 2 cm above the floor. Interruptions of the infrared light beams were recorded on electromechanical counters located at a distance from the activity cages and automatically printed every 10 min. The mice were placed individually in their cages and acclimatized to the cage for 30 min, were given vehicle, GBR 12909 (10 mg/kg) and/or apomorphine (0.05–2 mg/kg) and then returned for an additional 3-h test period.

2.3. Assay procedure

Dopamine, DOPAC and homovanillic acid (HVA) were measured as follows. The mice were decapitated 40 min after the administration of GBR 12909 (10 mg/kg) and/or apomorphine (0.05–2 mg/kg), when the effects of the drugs on locomotor activity were approximately at a peak. Control animals were treated with vehicle solution and killed on a similar schedule. The brain was quickly removed and dissected on an ice-cold glass plate into frontal cortex (excluding piriform cortex), nucleus accumbens (including olfactory tubercle) and striatum according to the method of Heffner et al. (1980), which was slightly modified. The brain parts were weighed and frozen on dry-ice and stored at −40°C until assayed. The tissue sample was homogenized in 0.1 M perchloric acid containing 5 mM EDTA and 3,4-dihydroxybenzylamine 25 pg/μl, using an ultrasonic cell disruptor (40% pulsed power for 30 s; Model 185, Branson), and centrifuged at 28 000 × *g* for 20 min at 4°C (KR-20000T, Kubota Seisakusho Co.). The supernatant was filtered through a 0.45-μm membrane filter (LC3A, Gelman Sciences) and a 20-μl aliquot of the filtered solution was injected into a high-performance liquid chromatography (HPLC) setup with electrochemical detection. The HPLC system consisted of a delivery pump (Waters 510, Waters Associates), a sample injector (WISP 710B, Waters Associates), a reverse phase column (250 mm length × 4.6 mm internal diameter; Eicompak MA-ODS, Eicom Co.), an electrochemical detector (LC-4B, Bioanalytical Systems Inc.) set at a potential of + 0.8 V versus an Ag/AgCl reference electrode and a computing integrator-printer (Waters 740, Waters Associates). The analytical column temperature was controlled at 40°C. The mobile phase consisted of 12% (v/v) methanol containing 0.1 M sodium acetate, 0.1 M citric acid, 0.23 mM sodium octydyl sulfate and 1.6 mM EDTA adjusted to pH 3.90, and was pumped through the column at a rate of 1 ml/min.

2.4. Drugs and solutions

1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine (GBR 12909) dihydrochloride and (−)-apomorphine hydrochloride were purchased from Research Biochemicals (Wayland, MA, USA).

GBR 12909 was dissolved in 0.9% saline solution. Apomorphine was dissolved in 0.1% ascorbic acid to stabilize its effects. All drugs were freshly prepared on the day of the experiment.

GBR 12909 was administered i.p. and apomorphine was injected s.c. in a volume of 5 ml/kg. GBR 12909 was given simultaneously when combined with apomorphine.

2.5. Statistical analysis

The data were analyzed by one-way analysis of variance (ANOVA) with the least significant difference test or Student's *t*-test. The results were considered statistically significant when P values were less than 0.05.

3. Results

3.1. Effects of GBR 12909, apomorphine and a combination of GBR 12909 with apomorphine on locomotor activity

The i.p. administration of GBR 12909 (10 mg/kg) significantly increased total locomotor counts for 3 h compared to the vehicle control (Fig. 1A). Fig. 2 shows the time course effects on locomotor activity. Locomotor activity induced by GBR 12909 was unchanged during the first 10 min, after which activity gradually increased, reaching a peak at 40 min, followed by a gradually declining but sustained hyperactivity throughout the recording (Fig. 2A). Movement was smooth, quick, and was accompanied by stereotyped rearing. A low dose of apomorphine (0.05 mg/kg s.c.) significantly decreased total locomotor counts for 40 min (Fig. 1B). In contrast, a high dose (2 mg/kg s.c.) produced a significant increase in locomotor activity (Fig. 1), which was characterized by an awkward and

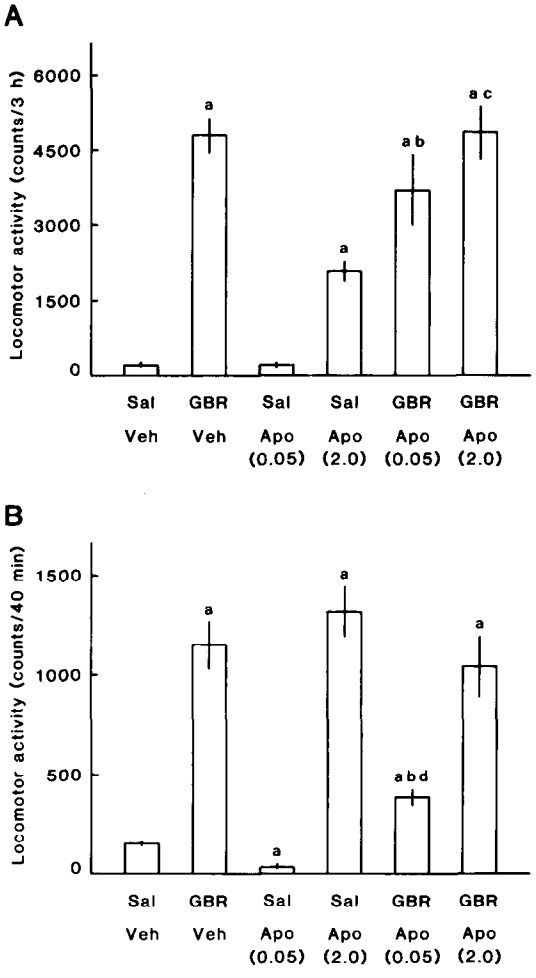

Fig. 1. Effects of GBR 12909 (GBR), apomorphine (Apo) and a combination of GBR 12909 with apomorphine on locomotor activity in mice. GBR 12909 (10 mg/kg) or saline (Sal) was administered i.p. Apomorphine (0.05 and 2 mg/kg) or vehicle (Veh) was injected s.c. GBR 12909 was given simultaneously when combined with apomorphine. Animals were allowed 30 min to acclimatize to the novel environment prior to the injection. The cumulative locomotor activity counts were determined as the total of each 10-min count up to 3 h (A) or 40 min (B). Each bar represents the mean ± S.E.M. ($n = 8$–9). [a] $P < 0.01$ versus saline + vehicle, [b] $P < 0.01$ versus saline + apomorphine (0.05 mg/kg), [c] $P < 0.01$ versus saline + apomorphine (2 mg/kg), [d] $P < 0.01$ versus GBR 12909 + vehicle, Student's t-test.

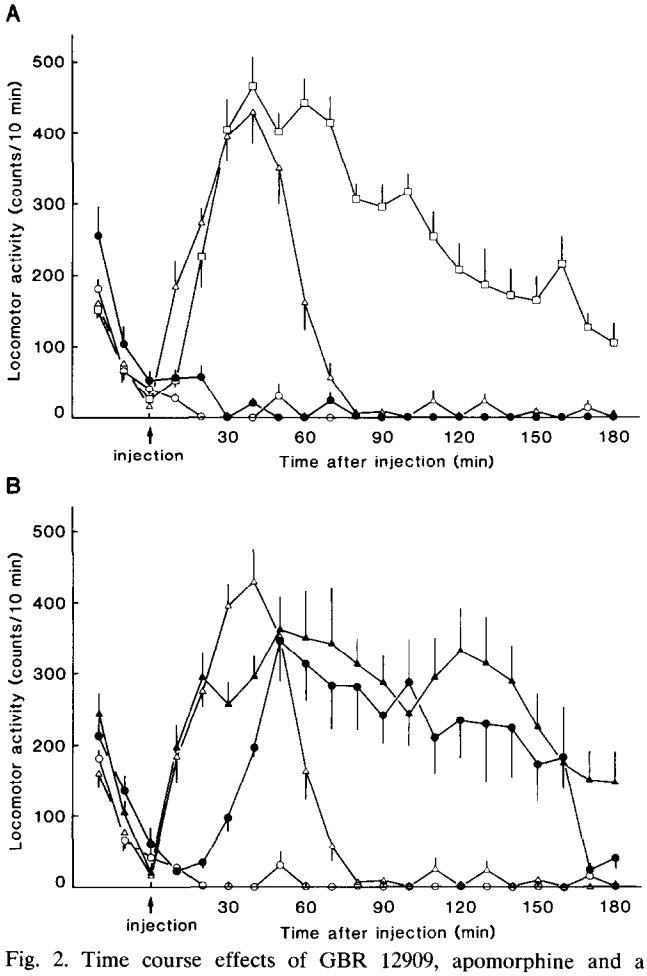

Fig. 2. Time course effects of GBR 12909, apomorphine and a combination of GBR 12909 with apomorphine on locomotor activity in mice. GBR 12909 (10 mg/kg) or saline was administered i.p. Apomorphine (0.05 and 2 mg/kg) or vehicle was injected s.c. GBR 12909 was given simultaneously when combined with apomorphine. Animals were allowed 30 min to acclimatize to the novel environment prior to the injection. Each point represents the mean ± S.E.M. ($n = 8$–9). In cases of points without a vertical bar, S.E.M. is within the symbol. (A) (●) Saline + vehicle; (□) GBR 12909 + vehicle; (○) saline + apomorphine (0.05 mg/kg); and (△) saline + apomorphine (2 mg/kg). (B) (○) Saline + apomorphine (0.05 mg/kg); (△) saline + apomorphine (2 mg/kg); (●) GBR 12909 + apomorphine (0.05 mg/kg); and (▲) GBR 12909 + apomorphine (2 mg/kg).

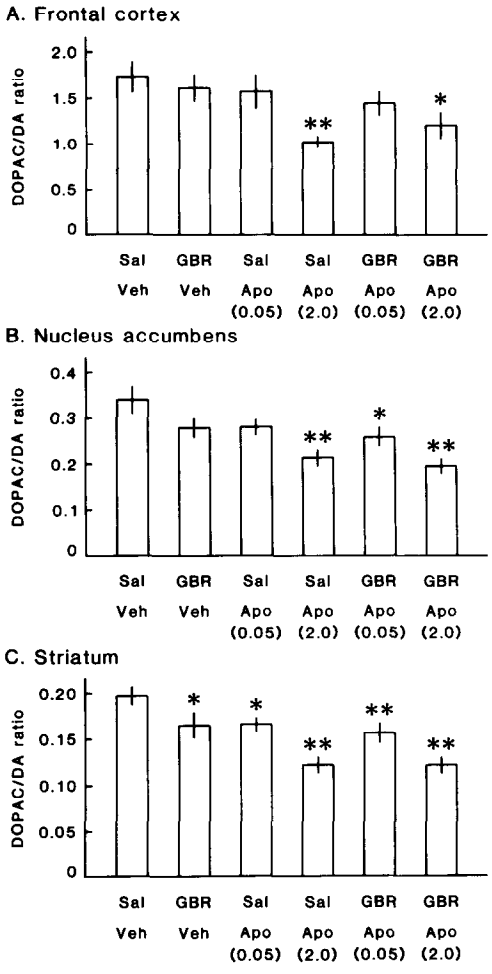

Fig. 3. Effects of GBR 12909 (GBR), apomorphine (Apo) and a combination of GBR 12909 with apomorphine on DOPAC/dopamine (DA) ratio in the frontal cortex (A), nucleus accumbens (B) and striatum (C) of mice. GBR 12909 (10 mg/kg) or saline (Sal) was administered i.p. Apomorphine (0.05 and 2 mg/kg) or vehicle (Veh) was injected s.c. GBR 12909 was given simultaneously when combined with apomorphine. Animals were decapitated 40 min after the administration of the drugs. Each bar represents the mean ± S.E.M. ($n = 8$). * $P < 0.05$, ** $P < 0.01$ compared to control animals, one-way ANOVA with least significant difference test.

slow gait compared to that after GBR 12909 (10 mg/kg). Locomotor activity soon increased after the administration, reaching a peak at 40 min. Thereafter the activity declined rapidly and reached the control level at 80 min after the injection (Fig. 2A).

GBR 12909 reversed the low-dose apomorphine-induced decrease in locomotor activity and significantly increased activity (Figs. 1 and 2B). However, GBR 12909 did not enhance the high-dose apomorphine-induced hyperlocomotion (Fig. 1B). The combination of GBR 12909 with a high dose of apomorphine soon produced hyperactivity after the injection. The movement was an awkward and slow gait characterized by high-dose apomorphine-induced behavior up to about the first 80 min. Thereafter this activity persisted for over 3 h, but the characteristics of movement changed into those induced by GBR 12909 (Fig. 2B).

3.2. Effects of GBR 12909, apomorphine and the combination of GBR 12909 with apomorphine on dopamine turnover

The levels of dopamine and its metabolites were examined 40 min after the administration of GBR 12909 and/or apomorphine, when the effects of the drugs on locomotor activity were approximately at a peak. Neither GBR 12909 (10 mg/kg i.p.) nor apomorphine (0.05 mg/kg s.c.) altered the DOPAC/dopamine ratio in the frontal cortex (Fig. 3A). In contrast, both GBR 12909 and a low dose of apomorphine had a tendency to decrease dopamine turnover to 82% of the vehicle control value in the nucleus accumbens (Fig. 3B) and significantly decreased the turnover to 84% in the striatum (Fig. 3C) at the same doses. A high dose of apomorphine (2 mg/kg s.c.) produced a significant decrease in the DOPAC/dopamine ratio to 59–63% in all brain regions. GBR 12909 did not modify the dopamine turnover change induced by both a low and a high dose of apomorphine in any brain region (Fig. 3). The HVA/dopamine ratio showed a similar tendency (data not shown).

The levels of dopamine did not change after any of the treatments in the frontal cortex, $F(5,42) = 0.36$, $P > 0.05$, nucleus accumbens, $F(5,42) = 0.91$, $P > 0.05$ and striatum, $F(5,42) = 0.30$, $P > 0.05$. Therefore, the changes in the levels of DOPAC mostly reflect those in

Table 1
Levels of dopamine in discrete brain regions, in ng/g wet weight of tissue

Region	Dopamine (ng/g tissue)					
	Sal + Veh	GBR + Veh	Sal + Apo (0.05)	Sal + Apo (2.0)	GBR + Apo (0.05)	GBR + Apo (2.0)
Frontal cortex	43 ± 6	35 ± 4	30 ± 2	35 ± 2	37 ± 5	43 ± 7
Nucleus accumbens	6987 ± 292	6953 ± 360	6949 ± 462	7275 ± 442	7799 ± 228	7389 ± 264
Striatum	11818 ± 588	11085 ± 300	11367 ± 521	11361 ± 417	11522 ± 346	11415 ± 409

GBR 12909 (GBR; 10 mg/kg) or saline (Sal) was administered i.p. Apomorphine (Apo; 0.05 and 2 mg/kg) or vehicle (Veh) was injected s.c. GBR 12909 was given simultaneously when combined with apomorphine. Mice were decapitated 40 min after the administration of the drugs. Values are means ± S.E.M. ($n = 8$).

the DOPAC/dopamine ratios. The concentrations of dopamine after each treatment in the discrete brain regions are shown in Table 1.

4. Discussion

GBR 12909, a potent and selective dopamine uptake inhibitor, has been shown to induce hyperlocomotion and stereotypy which are mediated by increased dopamine transmission (Heikkila and Manzino, 1984; Westerink et al., 1987). In the present study, we demonstrated that GBR 12909 reversed low-dose apomorphine-induced suppression in locomotor activity and significantly increased this activity (Figs. 1 and 2B). Despite the dramatic change in the behavior, GBR 12909 did not influence the low-dose apomorphine-induced alteration in the DOPAC/dopamine ratio, which is one of the indications of transmitter turnover (Fig. 3). These results suggest that a functional change via the stimulation of postsynaptic dopamine receptors does not necessarily lead to an alteration in dopamine turnover.

GBR 12909 is highly selective for the presynaptic dopamine transport complex and will elevate synaptic levels of endogenous dopamine by inhibiting the re-uptake of released dopamine. This may induce more physiological activation on dopamine neurons than do exogenous agonists. Therefore, GBR 12909 should prove to be a useful experimental tool.

It has been reported that selective and potent dopamine uptake inhibitors induce either an increase or no change in dopamine turnover in the striatum of rodents (Shore, 1976; Westerink et al., 1987). In contrast, we showed in this study that GBR 12909 alone, slightly but significantly, decreased dopamine turnover in the striatum (Fig. 3C). The reason for the discrepancy between these findings and our results is uncertain. However, it has been demonstrated that desipramine, a potent inhibitor of noradrenaline uptake, produces a reduction in noradrenaline turnover and causes a suppression of locus ceruleus cell firing by activating a neuronal feedback loop and somatodendritic autoreceptors in the locus (Cooper et al., 1991b). Additionally, Wy 25093, a selective and potent inhibitor of 5-hydroxytryptamine (5-HT) uptake, reduces 5-HT turnover rate (Diggory et al., 1981). These findings indicate that uptake inhibitors of noradrenaline and 5-HT have a similar effect on transmitter turnover. Therefore, this effect may apply to dopamine uptake inhibitors also, and these findings seem to support our results.

Dopaminergic mechanisms within the cortex, striatum and nucleus accumbens play an important role in the control of locomotor activity, although it is thought that the nucleus accumbens is primarily involved in the initiation and regulation of locomotor activity (Arnt, 1987). Therefore, we investigated the effects of GBR 12909 and apomorphine on locomotor activity and focused on dopamine turnover change in the frontal cortex, nucleus accumbens and striatum.

It was originally shown that dopaminergic mechanisms in the striatum were involved in stereotyped behavior, whereas the mesolimbic areas (the nucleus accumbens and the olfactory tubercle) were involved primarily in locomotor activity. More recently, however, intracerebral drug injections and lesion studies have revealed that both mesolimbic and nigrostriatal dopamine pathways and their terminal regions, particularly the nucleus accumbens and the striatum, mediate locomotor activity, although the nucleus accumbens is a more active site for the induction of locomotor activity than the striatum (Arnt, 1987; Fishman et al., 1983). Therefore, it is believed that GBR 12909 at 10 mg/kg may act on dopamine uptake sites in both mesolimbic and nigrostriatal dopamine neurons, because this dose of GBR 12909 produced both hyperlocomotion and stereotyped rearing. Hypomotility induced by a lower dose of apomorphine (0.05 mg/kg) may be mediated by autoreceptors either in mesolimbic dopamine pathways alone or in both mesolimbic and nigrostriatal dopamine pathways. A higher dose (2 mg/kg) may induce hyperlocomotion via postsynaptic dopamine receptors in the nucleus accumbens and/or the striatum. However, since the drugs used in this study were administered systemically, the precise nature of the mechanism is uncertain. To avoid this problem use of an intracerebral drug injection technique could be considered. However, this technique causes tissue damage and also has limitations in terms of specificity. Critical parameters are: selection of drug doses (which frequently have been very high) approximating the effective dose after peripheral injection, injection volume, and diffusion rates of test compounds (Arnt, 1987).

We demonstrated in this study that GBR 12909 reversed low-dose apomorphine (0.05 mg/kg s.c.)-induced hypomotility and significantly increased locomotor activity. It has been shown in a microdialysis study that administration of autoreceptor-selective doses of apomorphine (0.05–0.2 mg/kg s.c.) decreases the spontaneous release of dopamine by at most 50% (Zetterström and Ungerstedt, 1984). Since the low dose of apomorphine would not completely inhibit the spontaneous release of dopamine, GBR 12909 may gradually elevate synaptic levels of dopamine by inhibiting the re-uptake of the released dopamine. Consequently, the dopamine accumulated in the synaptic clefts due to GBR 12909 may stimulate the postsynaptic dopamine receptors and thus gradually increase locomotor activity.

Low doses of apomorphine cause significant decreases in the dopamine turnover in the striatum, ol-

factory tubercle, nucleus accumbens and piriform cortex, but not in the prefrontal cortex which lacks autoreceptors. This decrease in the turnover is mediated by activation of impulse-modulating somatodendritic autoreceptors. High doses produce larger decreases in the turnover in all brain regions via activation of negative neuronal feedback loops (Bannon et al., 1983; Chiodo et al., 1984; Zetterström and Ungerstedt, 1984). We have confirmed this in the present study again (Fig. 3).

As shown in this study, GBR 12909 did not enhance the high-dose apomorphine-induced hyperlocomotion in contrast to causing a dramatic change in the locomotion induced by a low dose of apomorphine (Figs. 1 and 2). The fact that GBR 12909 had no potentiation effect on behavior, in this case, may be ascribed to complete occupation by exogenous dopamine of postsynaptic receptors and reaching maximum activation of dopamine neurons. The combination of GBR 12909 with a high dose of apomorphine caused movements characteristic of high-dose apomorphine-induced behavior up to about 80 min after the injection, indicating that the effect of apomorphine was predominant. This may be explained by the fact that apomorphine has a much higher affinity for dopamine receptors than endogenous dopamine (Billard et al., 1984). After this, the movements characteristic for GBR 12909 became predominant. For the same reason, GBR 12909 may not cause any modulation in the dopamine turnover change induced by a high dose of apomorphine.

It is believed that low doses of apomorphine stimulate impulse-modulating somatodendritic autoreceptors and that GBR 12909 at doses which produce an increase in locomotion elevates synaptic levels of endogenous dopamine, stimulates postsynaptic dopamine receptors and may activate negative neuronal feedback loops. Moreover, we demonstrated that both a low dose of apomorphine alone and GBR 12909 alone significantly decreased the DOPAC/dopamine ratio, at least in the striatum. However, GBR 12909 did not influence low-dose apomorphine-induced dopamine turnover change in the nucleus accumbens and striatum. In contrast, GBR 12909 significantly changed the low-dose apomorphine-induced suppression of locomotion. The reason for the dissociation between a behavioral and a dopamine turnover change is uncertain. However, we considered the possible reasons for the dissociation. First, dopaminergic nerve terminals contain very large dopamine pools, but functionally available dopamine is believed to be a very small part of these. Therefore, the turnover may be difficult to change. Second, it may be that endogenous dopamine is not as effective on dopamine turnover as exogenous agonists. Finally, it may be that the mechanism of neuronal feedback loops caused by postsynaptic receptor stimulation is not as physiologically important as that of impulse modulation caused by somatodendritic autoreceptor activation.

Stimulation of dopamine autoreceptors in the cell bodies and dendrites within the A9 and A10 areas slows the firing rate of dopamine neurons, while stimulation of autoreceptors on the nerve terminals inhibits dopamine synthesis and release (Cooper et al., 1991a; Wolf and Roth, 1987). Dendrites of both A9 and A10 dopamine cells have the capacity for high-affinity uptake, storage and synthesis of dopamine, and have been found to release both previously taken up radiolabeled dopamine and endogenous dopamine (Wolf and Roth, 1987). Very high densities of dopamine transport complex are localized in the substantia nigra and ventral tegmental area (Dawson et al., 1986; Marcusson and Eriksson, 1988). GBR 12909 is, therefore, believed to act, not only on nerve terminals, but also on cell bodies and dendrites. Consequently, a low dose of apomorphine would activate both presynaptic and somatodendritic dopamine autoreceptors, resulting in diminished dopaminergic function. This may lead to decreased locomotor activity. We showed in this study that GBR 12909 at 10 mg/kg was sufficient to stimulate postsynaptic dopamine receptors behaviorally. However, GBR 12909 did not decrease dopamine turnover in the frontal cortex which lacks autoreceptors. GBR 12909 did not enhance the decrease in dopamine turnover induced by a low dose of apomorphine (which stimulates impulse-modulating autoreceptors within the A9 and A10 areas) in the nucleus accumbens and striatum either. Additionally, GBR 12909 and the low dose of apomorphine decreased dopamine turnover in the nucleus accumbens and striatum at the same dose, but not in the frontal cortex. These findings suggest that the GBR 12909-induced decrease in dopamine turnover in the nucleus accumbens and striatum may be mediated exclusively by activation of impulse-modulating somatodendritic autoreceptors. Furthermore, White and Wang (1986) have electrophysiologically shown that iontophoretically administered dopamine is significantly more potent to inhibit A10 dopamine cells than nucleus accumbens cells. Therefore, autoreceptors in the cell bodies and dendrites may play a rather important physiological role in dopamine turnover.

In conclusion, our study indicates that a behavioral change mediated by stimulation of postsynaptic dopamine receptors does not necessarily lead to an alteration in dopamine turnover.

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