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5-HT_{2C} receptor antagonists enhance the behavioural response to dopamine D_1 receptor agonists in the 6-hydroxydopamine-lesioned rat

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Abstract

Non-dopaminergic therapies are of potential interest in the treatment of Parkinson's disease given the complications associated with current dopamine-replacement therapies. In this study we demonstrate that SB 206553 (5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrol[2,3-f]indole) (20 mg/kg) enhanced the actions of the dopamine D_1 receptor agonist, SKF 82958 ((+)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide) (1 mg/kg), in eliciting locomotion in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. This action was only seen following prior priming with L-DOPA (L-3,4-dihydroxyphenylalanine). SB 206553 had no effect on rotational behaviour when given alone. 5-HT_{2C} receptor antagonists may have potential as a means of reducing reliance on dopamine replacement in the treatment of Parkinson's disease.

Keywords: Parkinson's disease; 6-Hydroxydopamine-lesioned rat; 5-HT_{2C} receptor; SKF 82958

1. Introduction

Dopamine replacement, with the precursor L-3,4-dihydroxyphenylalanine (L-DOPA), is the predominant treatment of Parkinson's disease. Unfortunately, long-term treatment results in the emergence of side effects. The severity of these side effects are related to the duration and cumulative dose of dopamine replacement (Nutt, 1990). Thus, a potentially useful strategy for the treatment of Parkinson's disease would be to define approaches that reduce the dose of dopamine replacement, or replace it entirely, yet still maintain full anti-parkinsonian efficacy (Brotchie, 1997).

Parkinsonian symptoms occur as a result of excessive inhibition of thalamo-cortical circuits secondary to overactivity of the substantia nigra pars reticulata and medial globus pallidus (Albin et al., 1989; Alexander et al., 1990; Brotchie et al., 1991). These structures together form the output regions of the basal ganglia. 5-HT_{2C} receptors are found in high concentrations within the substantia nigra pars reticulata (Pazos et al., 1987; Mengod et al., 1990) and are excitatory (Rick et al., 1995). Thus, stimulation of 5-HT_{2C} receptors may contribute to overactivity of the SNR in parkinsonism. We have previously demonstrated that the selective 5-HT_{2C} receptor antagonist, SB 206553 (5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrol[2,3-*f*]indole) (Forbes et al., 1995) induces a contraversive rotational response when infused into the substantia nigra pars reticulata on the dopamine-depleted side of the 6-hydroxydopamine-lesioned rat model of Parkinson's disease (Fox et al., 1998). Such behaviour represents a reduction in activity of basal ganglia outputs and can be taken as representing a potential anti-parkinsonian action. No rotational response was seen following infusion into the dopamine-intact side, suggesting that activation of 5-HT_{2C} receptors in the substantia nigra pars reticulata occurs in the parkinsonian but not the normal basal ganglia. In keeping with this idea that abnormalities of 5-HT_{2C} transmission within the substantia nigra pars reticulata may occur in parkinsonism are our preliminary findings that 5-HT_{2C} receptor binding is increased in patients with Parkinson's disease (Fox and Brotchie, 1996b). In addition, systemic administration of selective 5-HT_{2C} receptor antagonists, normethylclozapine, SB 200646A (*N*-(1-methyl-5-indolyl)-*N*′-(3-pyridyl)urea hydrochloride) or SB 206553, enhances the action of the dopamine D_2 receptor

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agonist, quinpirole in the 6-hydroxydopamine-lesioned rat (Fox and Brotchie, 1996a; Fox et al., 1998).

Current directly acting dopamine receptor agonists used in the treatment of Parkinson's disease predominantly act at dopamine D_2 receptors, e.g. ropinirole, cabergoline, pramipexole (Watts, 1997). However, there is growing evidence that dopamine D_1 receptor agonists may also be useful in the treatment of Parkinson's disease (Blanchet et al., 1993; Brefel et al., 1997). Indeed, the greater efficacy of L-DOPA over selective dopamine D_2 receptor agonists may be a result of a synergistic effect of dopamine D_1 and D_2 receptor-mediated action (Walters et al., 1987).

In this study, we investigate the ability of the selective 5-HT_{2C} receptor antagonist, SB 206553 to enhance the anti-parkinsonian action of the dopamine D_1 receptor agonist, SKF 82958 ((+)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide) (O'Boyle et al., 1989).

2. Materials and methods

2.1. 6-Hydroxydopamine lesioning

Male Sprague–Dawley rats (260–280 g, Manchester University, BSU) were anaesthetised with sodium pentobarbitone (60 mg/kg i.p.), 30 min following pre-medication with pargyline (5 mg/kg) and desiprimine (25 mg/kg). 12.5 μg of 6-hydroxydopamine · HCl (in 2.5 μl, 0.02% ascorbic acid) was then infused into the right medial forebrain bundle, using routine stereotaxic procedures (co-ordinates, +2 mm right, −2.8 mm posterior, 9 mm vertical to skull from bregma, according to Paxinos and Watson, 1996). Infusions were made manually with a 26-gauge Hamilton syringe over 5 min, the needle was left in place for a further 1 min before withdrawal. The animals were housed in groups of four under temperature-controlled conditions (19–21°C), with 12 h alternating light/dark cycles (0800–2000 h lights on). Food and water were available ad libitum.

2.2. Behavioural assessment

The animals were allowed a recovery period of 3 weeks post-surgery. The behavioural effects of appropriate vehicle, SB 206553 and/or SKF 82958 were then assessed. Behavioural testing was performed between 1100 and 1500 h. Animals were assigned to treatment groups at random. SB 206553 (20 mg/kg s.c) or appropriate vehicle, was injected 20 min prior to behavioural testing ($t - 20$ min). SKF 82958 (0.1 mg/kg i.p.) was injected at $t = 0$. The animals were placed into hemispherical stainless-steel bowls (50 cm diameter) at $t = 0$ min and their behaviour videotaped for 2 h. The animals were not disturbed during the experimental period. The number of net rotations contraversive to the side of the 6-hydroxydopamine lesion in each 5-min time bin were counted by post hoc analysis of the videotapes.

Three days later, the animals were injected with L-DOPA-methyl ester (50 mg/kg i.p.) and the peripheral dopa-decarboxylase inhibitor, benserazide (25 mg/kg i.p.). The rotational behaviour was assessed, as described above, between 30 and 90 min post-injection. Animals showing less than 200 rotations per hour contraversive to the side of the 6-hydroxydopamine lesion were rejected from the statistical analysis. Three days later, following this 'priming' with L-DOPA-methyl ester, a second injection of vehicle/SB 206553 and /or SKF 82958 was given. The rotational behaviour was assessed as described above, for the period, 0–120 min post-injection.

2.3. Drugs

Pargyline, desiprimine, 6-hydroxydopamine · HCl, L-DOPA-methyl ester and benserazide (Sigma, UK) and SKF 82958 (Research Biochemicals, USA) were all dissolved in sterile water. SB 206553 (gift from Dr. T. Blackburn, SmithKline Beecham Pharmaceuticals), was given as a suspension in 8% hydroxypropyl-β-cyclodextrin (w/w) and 10% polyethylene glycol (w/v). All injection volumes were 1 ml/kg.

2.4. Statistical analysis

Statistical analysis of rotational scores was carried out using a one way analysis of variance, ANOVA, followed by post hoc Student–Newman–Keuls analysis. All statistical analyses were performed on the 1-h period, 30–90 min post-drug administration.

3. Results

3.1. 6-Hydroxydopamine lesion efficacy

All animals included in the statistical analysis showed greater than 200 rotations per hour contraversive to the 6-hydroxydopamine lesion, following treatment with L-DOPA-methyl ester (50 mg/kg) and benserazide (25 mg/kg). Mean rotations contraversive to the lesioned side were 371.0 ± 16.7 per hour. The mean rotational response was not significantly different between any treatment group, $P > 0.05$, ANOVA, $F(3,19) = 0.2349$, unprimed groups and $P > 0.05$, ANOVA, $F(3,16) = 0.9051$ primed groups.

3.2. Behavioural effects of SB 206553 alone and in combination with SKF 82958

In the previously untreated (unprimed state), significant effects of treatment were seen ($P < 0.05$, ANOVA, $F(3,19) = 7.485$) (Fig. 1a and b). There was no significant

difference in the rotational response after administration of SB 206553 (20 mg/kg) compared to vehicle (-2.0 ± 1.3 ($n = 6$) and -4.8 ± 1.87 ($n = 6$) net rotations contraversive to the lesioned side per hour, respectively; $P > 0.05$, Student–Newman–Keuls test). SKF 82958 (0.1 mg/kg) elicited a contraversive rotational response (172.0 ± 44.9 net rotations contraversive to the lesioned side per hour, ($n = 5$)) this was significantly different to vehicle ($P < 0.05$). Co-administration of SKF 82958 and SB 206553 elicited 217.5 ± 72.2 net rotations contraversive to the lesioned side per hour ($n = 6$), which was significantly greater than vehicle ($P < 0.01$), but not to SKF 82958 alone ($P > 0.05$).

Following priming with L-DOPA methyl ester, significant effects of treatment were seen ($P < 0.0001$, ANOVA, $F(3,16) = 29.728$) (Fig. 2a and b). The rotational response elicited by SB 206553 was not significantly different to vehicle (-0.2 ± 0.8 ($n = 5$) and -2.8 ± 0.8 ($n = 5$) net rotations contraversive to the lesioned side per hour, respectively, $P > 0.05$). SKF 82958 elicited a marked contraversive rotational response (696.4 ± 149.2 net rotations contraversive to the lesioned side per hour ($n = 5$)) that was significantly greater than vehicle, ($P < 0.001$). Co-administration of SB 206553 with SKF 82958 produced a significantly greater rotational response (1044.4 ± 121.3 net rotations contraversive to the lesioned side per hour ($n = 5$)) than SKF 82958 alone ($P < 0.05$).

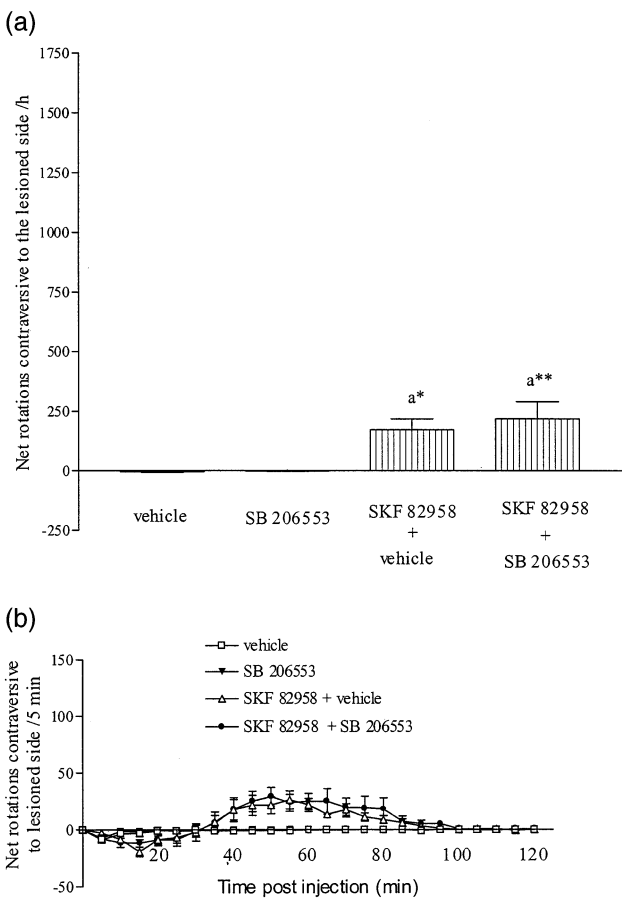

Fig. 1. The behavioural response to systemic administration of the 5-HT_{2C} receptor antagonist, SB 206553 (20 mg/kg s.c.) alone or in combination with the dopamine D_1 receptor agonist, SKF 82958 (0.1 mg/kg i.p.) in the previously untreated (unprimed) unilateral 6-hydroxydopamine-lesioned rat model of Parkinson's disease. (a) Represents mean total net contraversive rotations over 60 min ± S.E.M. (time 30–90 min post injection) ($n = 5$–6), a = compared to vehicle, $^{*}P < 0.05$, $^{**}P < 0.01$, ANOVA, post hoc Student–Newman–Keuls. (b) Represents the time course of rotational behaviour; data represent mean total net rotations contraversive to the 6-hydroxydopamine-lesioned side per 5-min time bin ± S.E.M.

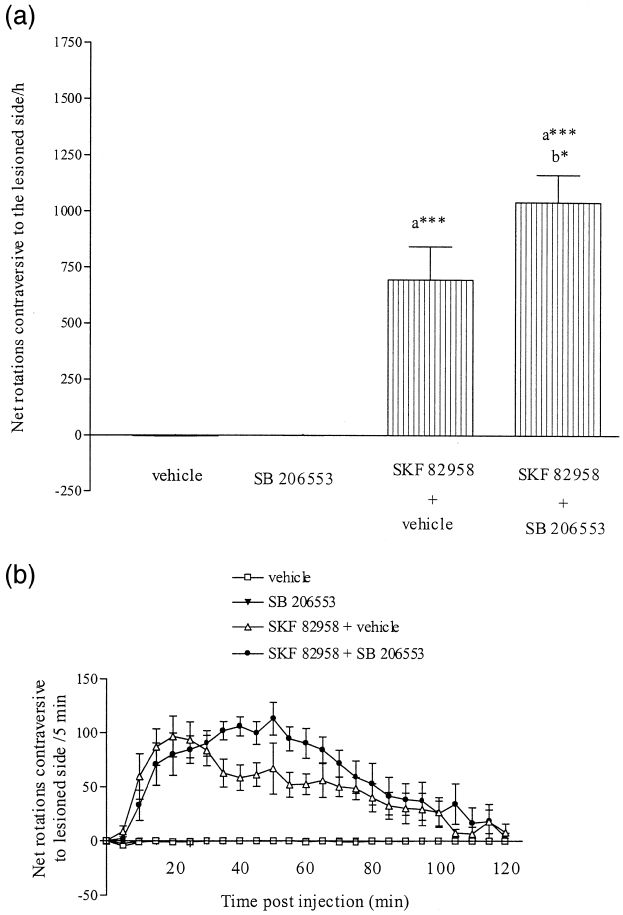

Fig. 2. The behavioural response to systemic administration of the 5-HT_{2C} receptor antagonist, SB 206553 (20 mg/kg s.c.) alone or in combination with the dopamine D_1 receptor agonist, SKF 82958 (0.1 mg/kg i.p.) in the unilateral 6-hydroxydopamine-lesioned rat model of Parkinson's disease following a 'priming' dose of L-DOPA-methyl ester. (a) Represents mean total net contraversive rotations over 60 min ± S.E.M. (time 30–90 min post injection) ($n = 5$), a = compared to vehicle, b = compared to SKF 82958 + vehicle, $^{*}P < 0.05$, $^{***}P < 0.001$ ANOVA, post hoc Student–Newman–Keuls. (b) Represents the time course of rotational behaviour; data represent mean total net rotations contraversive to the 6-hydroxydopamine-lesioned side per 5-min time bin ± S.E.M.

4. Discussion

4.1. Methodological considerations

All animals included in the statistical analysis had a behavioural response of greater than 200 rotations con-

traversive to the lesioned side per hour following challenge with L-DOPA methyl ester (100 mg/kg). This has previously been shown to indicate greater than 90% loss of striatal dopaminergic terminals, as measured by tyrosine hydroxylase immunoreactivity and [^{3}H] mazindol binding (Papa et al., 1994; Thomas et al., 1994; Duty and Brotchie, 1997). There was no significant difference in the rotational behaviour following L-DOPA challenge between any of the groups. Thus, there was no difference in the degree of dopamine depletion that might account for changes seen in the behaviour following test drug treatment. The dose of SB 206553 used in the experiment was that which had been previously demonstrated to antagonise 1-(3-chlorophenyl) piperazine-induced hypolocomotion, a 5-HT$_{2C}$ receptor mediated effect (Kennett and Curzon, 1988; Kennett et al., 1994, 1996). Higher doses were not used to avoid loss of receptor selectivity.

This study also indicates the importance of timing of L-DOPA administration in behavioural experimental paradigms. The effect of priming with a single dose of L-DOPA was to increase the number of rotations contraversive to the 6-hydroxydopamine-lesioned side, following challenge with the dopamine D$_1$ receptor agonist. Thus, there is a marked difference in the behaviour pre- and post-L-DOPA. The priming of dopamine D$_1$ receptor-mediated behaviour, following prior treatment with L-DOPA, has been noted by previous workers, using the partial dopamine D$_1$ receptor agonist, SKF 38393 (±)1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrochloride) (Morelli and DiChiara, 1987). The mechanism underlying priming is thought to involve an increase in the phosphorylation of dopamine and cAMP-regulated phosphoprotein (DARPP-32) (Barone et al., 1994). Thus, changes in signal transduction following dopamine D$_1$ receptor stimulation underlie priming rather than any change in the number or affinity of the receptor (Morelli et al., 1990).

4.2. Dopamine D$_1$ receptor agonists in the 6-hydroxydopamine-lesioned rat

The dopamine D$_1$ receptor agonist SKF 82958 elicited a rotational response contraversive to the lesioned side in the unprimed 6-hydroxydopamine-lesioned rat. Other workers have failed to elicit such a rotational effect with dopamine D$_1$ receptor agonists in previously untreated animals, but did elicit a significant rotational response following priming with L-DOPA (Morelli and DiChiara, 1987; Morelli et al., 1989). This lack of effect in previous studies is probably due to the use of SKF 38393, which is a partial dopamine D$_1$ receptor agonist having only 20–50% of the intrinsic activity of dopamine in vitro compared to 149% activity with SKF 82958 (Arnt et al, 1988; O'Boyle et al.,1989).

In the 6-hydroxydopamine-lesioned rat, a response to systemically administered dopamine agonists characterised by rotation contraversive to the lesioned side is usually the result of stimulating up-regulated receptors on the lesioned side. However, unlike dopamine D$_2$ receptors, there is no increase in number or affinity of dopamine D$_1$ receptors in the striatum on the 6-hydroxydopamine-lesioned side (Pimoule et al., 1985). It has been suggested that alterations in the dopamine D$_1$ receptor signal transduction mechanisms following 6-hydroxydopamine-lesioning may play a role in mediating rotational behaviour (Huang and Walters, 1994). Dopamine D$_1$ receptor activation increases in firing of the GABAergic striato-nigral pathway. This leads to inhibition of the substantia nigra pars reticulata/medial globus pallidus and a contraversive rotational response (Trugman and Wooten, 1987; Weick et al., 1990).

The rotational response elicited by SKF 82958 (either with vehicle or with SB 206553) in the unprimed state, was ipsiversive to the lesioned side for the first 30 min and then reversed direction. The mechanism of this behavioural effect is unclear, but may involve dopamine preferentially acting on dopamine D$_1$ receptors on the unlesioned side, initially to cause a rotational response ipsiversive to the lesioned side. Similar behavioural responses are noted following de novo treatment of 6-hydroxydopamine-lesioned rats with low dose L-DOPA (Henry et al., 1998).

4.3. The anti-parkinsonian action of 5-HT$_{2C}$ receptor antagonists

The responses to combined SB 206553 and SKF 82958 treatment were reminiscent of those seen with SB 206553 and the dopamine D$_2$ receptor agonist, quinpirole (Fox et al., 1998). Furthermore, the effects are similar to those previously reported with quinpirole and normethylclozapine, also a 5-HT$_{2C}$ receptor antagonist (Fox and Brotchie, 1996a). Thus, 5-HT$_{2C}$ receptor antagonists are able to enhance the anti-parkinsonian action of both dopamine D$_1$ and D$_2$ receptor agonists. At the doses used, SB 206553 was unable to elicit an anti-parkinsonian action alone, as has been previously demonstrated (Fox and Brotchie, 1996a; Fox et al., 1998). The lack of effect may simply be due to an insufficient dose. However, more importantly, higher doses were not used as this may have resulted in loss of receptor subtype selectivity. The behavioural effects observed in the present study are thus likely to be due to a 5-HT$_{2C}$ receptor-mediated action. This lack of efficacy of 5-HT$_{2C}$ receptor antagonists administered alone in the 6-hydroxydopamine-lesioned rat is not due to an action on the unlesioned substantia nigra pars reticulata that would counter effects on the lesioned side because infusion of SB 206553 into the substantia nigra pars reticulata on the unlesioned side of a 6-hydroxydopamine lesioned rat does not elicit any rotational response (Fox et al., 1998). In keeping with this, previous workers using a number of selective 5-HT$_{2C}$ receptor antagonists, SB 200646A, SB 206553 and SB 242084 have shown that

these compounds do not elicit locomotor activity when given alone (Kennett et al, 1994, 1996, 1997).

The exact nature of the interaction between SB 206553 and SKF 82958 cannot be determined from this study. Thus, at present it is not clear whether the effects described here represent an increase in the maximal effects of dopamine D_1 receptor stimulation or a leftward shift in the dose–response curve for the action of dopamine D_1 receptor stimulation. Further studies of the full dose–response relationship will be required to address this issue. In addition, pharmacokinetic factors cannot be excluded as a mechanism whereby SB 206553 enhances the effects of SKF 82958. Further studies assessing plasma and/or brain concentrations of SKF 82958 will be required to address this issue.

The mechanism whereby 5-HT_{2C} receptor antagonists enhance the anti-parkinsonian action of dopamine receptor agonists may involve reducing the overactivity of the substantia nigra pars reticulata/medial globus pallidus. When given alone, 5-HT_{2C} receptor antagonists may only be able to reduce the activity to a certain degree following systemic administration. There may therefore not be sufficient reduction in the activity of the substantia nigra pars reticulata to restore the normal thalamo-cortical output and have an overt anti-parkinsonian effect. An additional action of dopamine receptor agonists to further reduce substantia nigra pars reticulata activity may be required to produce a significant rotational response contraversive to the lesioned side, in the 6-hydroxydopamine lesioned rat. In a similar way, a synergistic effect of dopamine replacement and reducing overactivity within the substantia nigra pars reticulata has also been seen with the *N*-methyl-D-aspartate (NMDA) receptor antagonist, MK-801((+)-5-methyl-10,11-dihydro-5*H*-dibenzo(*a*,*d*)-cyclohepten-5,10-imine maleate) in the monoamine-depleted rat model of Parkinson's disease (Klockgether and Turski, 1990; Loschmann et al., 1991; Fenu et al, 1995).

These findings suggest that 5-HT_{2C} receptor antagonists are potentially useful in the treatment of early Parkinson's' disease as 5-HT_{2C} receptor antagonists may enhance the anti-parkinsonian action of both dopamine D_1 and D_2 receptor agonists. It is current clinical practice to initiate treatment with a dopamine receptor agonist to minimise long-term side effects of L-DOPA. However, such agents often have poorer anti-parkinsonian efficacy compared to L-DOPA (Hely et al., 1994; Rascol et al., 1998). Thus, additional use of a 5-HT_{2C} receptor antagonist in combination with a dopamine receptor agonist may be clinically beneficial. In addition, 5-HT_{2C} receptor antagonists might be expected to enhance the anti-parkinsonian actions of L-DOPA as these result from stimulation of both dopamine D_1 and dopamine D_2 receptors. However, a specific study will be needed to address the issue of the interaction of 5-HT_{2C} receptor antagonists and L-DOPA as the interaction between subtype selective dopaminergic agents and non-dopaminergic agents do not reliably predict their interactions with L-DOPA. For instance, the NMDA antagonist MK801 attenuates the anti-parkinsonian actions of D_2 receptor stimulation but enhances the anti-parkinsonian actions of L-DOPA (Morelli and DiChiara, 1990).

In conclusion, the use of 5-HT_{2C} receptor antagonists in Parkinson's disease may reduce the reliance upon dopamine replacement therapies and may thus reduce the problems associated with long term use of currently available anti-parkinsonian agents.

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