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Role of dopamine D_1 and D_2 receptors in the nucleus accumbens in jaw movements of rats: a critical role of the shell

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Abstract

Given the differences in the dopamine neurotransmission between the shell and the core of the nucleus accumbens, as well as the differential involvement of these two domains in oral behaviour of rats, it was decided to determine whether or not dopamine D_1 and/or dopamine D_2 receptors differentially direct oral behaviour in these two domains in rats. Intra-accumbens injections of the dopamine D_1 receptor agonist (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SKF 82958: 5 μg/0.2 μl), the dopamine D_2 receptor agonist quinpirole (10 μg/0.2 μl) and their combination were used to assess the role of these accumbens domains in jaw movements of rats. The present study shows that the combined administration of SKF 82958 and quinpirole into the shell, but not the core, of the nucleus accumbens produced a highly significant increase in jaw movements, when doses which per se were nearly ineffective, were injected. This effect was fully inhibited by prior administration of either the dopamine D_1 receptor antagonist *R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390: 0.5 μg/0.2 μg) or the dopamine D_2 receptor antagonist (−)-sulpiride (25 ng/0.5 μl) into the same region. It is concluded that dopamine D_1 *and* D_2 receptors in the shell, but not the core, of the nucleus accumbens are involved in jaw movements of the rat, providing the first piece of evidence that dopamine D_1 and D_2 receptors in the shell of the nucleus accumbens mediate a particular behaviour.

Keywords: Nucleus accumbens, shell, core; Dopamine D_1 receptor; Dopamine D_2 receptor; SKF 82958; Quinpirole; SCH 23390; (−)-Sulpiride; Jaw movement; (Rat)

1. Introduction

The nucleus accumbens is considered a neural interface between the limbic system and the extrapyramidal system (Mogenson and Yim, 1981; Cools, 1988). Today, evidence suggests that it is involved in the reinforcing effects of drugs as well as in the programming of ongoing behaviour. For example, decreases in self-administration of psychostimulants have been observed after intra-accumbens injections of dopamine D_2 receptor antagonists, suggesting that this structure plays a critical role as neuroanatomical substrate for drug reinforcement in rats (Robledo et al., 1992). Also, recent data show that the combined injection of the dopamine D_1 receptor agonist SKF 38393 together with the dopamine D_2 receptor agonist quinpirole into the nucleus accumbens enhances oral behaviour in rats (Koshikawa et al., 1990; Prinssen et al., 1992; Koene et al., 1993). This suggests a critical role as neuroanatomical substrate for oral behaviour in rats.

Recently, it has become evident that the nucleus accumbens is a heterogeneous structure. At least two different parts can be discerned: the shell and the core (Voorn et al., 1986; Groenewegen et al., 1987; Heimer et al., 1991; Zahm and Brog, 1992; Brog et al., 1993; Meredith et al., 1993; Jongen-Rêlo et al., 1994). The shell and the core appear to be innervated by different sets of dopaminergic neurons (Voorn et al., 1986; Zahm, 1991, 1992). The shell contains a richer dopamine plexus than the core (Voorn et al., 1986), and the concentration of dopamine in the shell is higher than that in the core (Deutch and Cameron, 1992). The shell is less vulnerable to the neurotoxic

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6-hydroxydopamine than the core (Deutch and Cameron, 1992). The dopamine turnover in the shell is more sensitive to restraint stress than that in the core, whereas the dopamine utilization in the shell is less sensitive to haloperidol than that in the core (Deutch and Cameron, 1992). Furthermore, the dopamine D_1 binding in the rostral areas of the nucleus accumbens appears to be higher in the shell than in the core, whereas the dopamine D_2 binding appears to be lower in the shell than in the core (Bardo and Hammer, 1991; Jongen-Rêlo et al., 1992). These data suggest that functional differences in the dopamine neurotransmission occur in the two domains. Indeed, electrophysiological studies show that the synaptic transmission is differentially modulated by dopamine in the shell and the core (Pennartz et al., 1992).

Recent lesion studies suggest that especially the shell may be important in processing the reward reinforcing actions of psychostimulants such as cocaine (Robledo and Koob, 1993). In addition, recent studies on oral behaviour suggest that especially the shell plays a critical role as neuroanatomical substrate for oral behaviour (Cools et al., 1993; Prinssen et al., 1994).

Given the differences in the dopamine neurotransmission between the shell and the core, as well as the differential involvement of these two domains in oral behaviour, the purpose of the present study was to determine whether or not dopamine D_1 and/or dopamine D_2 receptors differentially modulate oral behaviour in these two domains. Since previous studies have shown that intra-accumbens administration of a highly specific dose combination of the dopamine D_1 receptor agonist (±)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol (SKF 38393: 5 μg) and the dopamine D_2 receptor agonist quinpirole (10 μg) was necessary for eliciting a well-defined type of jaw movements marked by muscle-specific electromyographic activities of the anterior digastric and masseter muscle (Koshikawa et al., 1991a), this combination of doses was chosen for the present study. The volume, however, was reduced from 0.5 μl to 0.2 μl in order to limit the diffusion to the chosen domains as good as possible. The dopamine D_1 receptor antagonist SCH 23390 and the dopamine D_2 receptor antagonist (−)-sulpiride were used to study the possible involvement of dopamine D_1 and D_2 receptors in the effects observed.

Recording of jaw openings by means of a light-emitting diode attached to the mandible of anaesthetized rats was used to analyze the effects of dopaminergic agents upon oral behaviour. This method has been found to be a valid method for studying the anatomical and pharmacological substrate of apomorphine-induced jaw movements. This method has provided reliable data about the nature of the functional interaction between dopamine D_1 and D_2 receptors in apomorphine-induced jaw movements (Koshikawa et al., 1990), and it has provided detailed information about the differential involvement of the nucleus accumbens, the dorsal and ventral striatum as well as the globus pallidus in apomorphine-induced jaw movements (Koshikawa et al., 1990, 1991a,b).

2. Materials and methods

2.1. Surgical procedures

Male Sprague-Dawley rats (260–330 g) were anaesthetized with ketamine HCl (10 mg/kg i.p.), supplemented during surgery with halothane (0.5–4% when appropriate). The surgical and recording procedures were as described previously (Koshikawa et al., 1990). A small light-emitting diode was fixed to the mandible, and the animal held in a stereotaxic frame so that the head was fixed in constant relation to a light-sensitive transducer which detected the vertical movements of the diode. The spinal cord was transected at C1 level to confine drug-induced movements to the head region, jaw movements were recorded on a polygraph for later quantification: jaw movements were counted automatically with a spike trigger. The registration period lasted 240 min. Guide cannulas were implanted bilaterally into the shell or into the core of the nucleus accumbens according to previously described procedures (Prinssen et al., 1994). The coordinates based on the atlas of Paxinos and Watson (1986) were: anterior = 10.6 mm, lateral = 0.5 mm, vertical = 8.0 mm (shell); anterior = 10.6 mm, lateral = 1.2 mm, ventral = 7.0 mm (core). Cannulas (0.5 mm o.d., 0.3 mm i.d., 6.0 mm length) directed at the shell were angled 21 degrees, and cannulas directed at the core were angled 18 degrees from the mid sagittal plane to avoid the ventricular system. The injection volume which was 0.2 μl per side unless otherwise indicated, was delivered over a 20 s period, and the needle was left in situ for an additional 20 s period after completion of the injection. To minimize potential damage to the target site by the implanted guide cannula the vertical coordinates of the tip were chosen dorsal to the intended site of injection; the injection needle, 31-gauge stainless steel, was exactly 1.2 mm (for the core) or 2.0 mm (for the shell) longer than the implanted guide cannula. After surgery, animals were maintained under anaesthesia by continuous infusion of ketamine (10 mg/h i.v.). Lignocaine HCl (2%) gel was applied to all incisions, and the rectal temperature was maintained at 37°C with a thermostatically controlled heating pad.

2.2. Drugs

The animals ($n = 6$–12 per experiment) received bilateral injections of the dopamine D_1 receptor ago-

nist SKF 82958 hydrochloride (5 μg; Research Biochemicals), the dopamine D_2 receptor agonist quinpirole (10 μg; Research Biochemicals) or their combination (cocktail); control animals received the solvent, namely saline. In an additional set of experiments the dopamine D_1 receptor antagonist SCH 23390 maleate (0.5 μg/0.2 μl, $n = 6$; Schering) was given 10 min prior to the SKF 82958-quinpirole mixture in order to assess the contribution of dopamine D_1 receptors to the effects observed. In two final sets of experiments intra-accumbens injections of the selective dopamine D_2 receptor antagonist (−)-sulpiride (25 ng/0.2 μl, $n = 6$; 25 ng/0.5 μl, $n = 6$; Ravizza) were given 30 min prior to the combination of SKF 82958 and quinpirole in order to assess the contribution of dopamine D_2 receptors to the effects observed. Doses and time schedule were based on previously published studies (Koshikawa et al., 1990; Prinssen et al., 1992; Koene et al., 1993). Animals were used only once.

At the end of the experiments, rats were deeply anaesthetized with pentobarbitone Na, perfused transcardially with 10% formaldehyde solution, and the brains were removed. Injection sites were identified from 50 μm coronal sections stained with Nissl. Data were analyzed for only those animals in which the injections were correctly placed.

2.3. Statistical analysis

All values are expressed as means ± S.E.M. The effects were analyzed with a two-way analysis of variance (ANOVA) with a mixed design for repeated measures in time, including the univariate ANOVA test with 'Greenhouser-Geisser Epsilon' correction for the factor time.

3. Results

3.1. Effects of the combined injection of SKF 82958 and quinpirole into the core and the shell of the nucleus accumbens

Fig. 1 (left side) gives a survey of the core and shell region in which the injection sites were located; data of rats with injection sites outside the arced region were discarded in the analysis ($n = 35$). Fig. 1 (right side) provides all injection sites in the shell of rats treated with the cocktail of SKF 82958 and quinpirole (upper part) and all injection sites in the core of rats treated with this cocktail (lower part).

The overall effects of saline (control; $n = 6$/core; $n = 7$/shell), SKF 82958 ($n = 6$/shell), quinpirole ($n = 6$/shell) and their combination ($n = 6$/core; $n = 6$/shell) are shown in Fig. 2. The combined administration of SKF 82958 and quinpirole was ineffective, when injected into the core: the number of jaw movements in the treated rats did not significantly differ from that in solvent treated animals ($F(1,10) = 0.10$, $P = 0.76$). Since previous studies have shown that these drugs only potentiate, but not counteract, each other's effects after administration into the nucleus accumbens and, in addition, have no effects per se after administration into the nucleus accumbens (Koshikawa et al., 1990), no attempts were done to investigate the effects of injections of each drug separately into the core. In contrast, the combined injection of SKF 82958 and quinpirole was highly effective, when injected into the shell: the number of jaw movements was significantly greater than that found in solvent-treated rats ($F(1,11) = 24.34$, $P < 0.001$). When given alone in the same dose, SKF 82958 remained ineffective following injections into the shell: the number of jaw movements in the SKF-treated rats did not differ from that found in solvent-treated rats ($F(1,11) = 2.92$, $P = 0.12$). The number of jaw movements in quinpirole-treated rats, however, was significantly greater than that found in solvent-treated rats ($F(1,11) = 10.01$, $P < 0.009$); however, Figs. 2 and 3 show that there was only a minor increase. Comparing the effects of the combined treatment with the effects of each single drug resulted in a highly significant difference (SKF 82958 + quinpirole versus quinpirole: $F(1,10) = 10.16$, $P < 0.01$; SKF 828958 + quinpirole versus SKF 828958: $F(1,10) = 15.27$, $P < 0.003$).

The time-dependent effects of the combined injections of SKF 82958 and quinpirole into the core respectively the shell are shown in Fig. 3. This figure clearly shows that the effect started nearly immediately after the injection into the shell, reached its peak around 60 min and vanished about 120 min after the injection: apart from the fact that there was a significant drug effect (see above), there was a significant time effect ($F(9,99) = 5.99$, $P < 0.001$) as well as a significant interaction between the factor drug and the factor time ($F(9,99) = 5.75$, $P < 0.001$).

3.2. Effects of SCH 23390 and (−)-sulpiride upon jaw movements elicited by the combined administration of SKF 82958 and quinpirole into the nucleus accumbens

Injections of SCH 23390 (0.5 μg) into the shell significantly attenuated the shell effects of the cocktail of SKF 82958 and quinpirole (Fig. 4; $F(9,99) = 3.60$, $P < 0.001$; $n = 6$).

Injections of (−)-sulpiride (25 ng) into the shell significantly attenuated the shell effects of the cocktail of SKF 82958 and quinpirole only, when (−)-sulpiride was dissolved in 0.5 μl (Fig. 4; $F(1,10) = 6.68$, $P < 0.03$; $n = 6$). Such injections remained ineffective, when 25 ng (−)-sulpiride was injected in a volume of 0.2 μl ($F(1,10) = 1.18$, $P < 0.3$; $n = 6$). However, this treat-

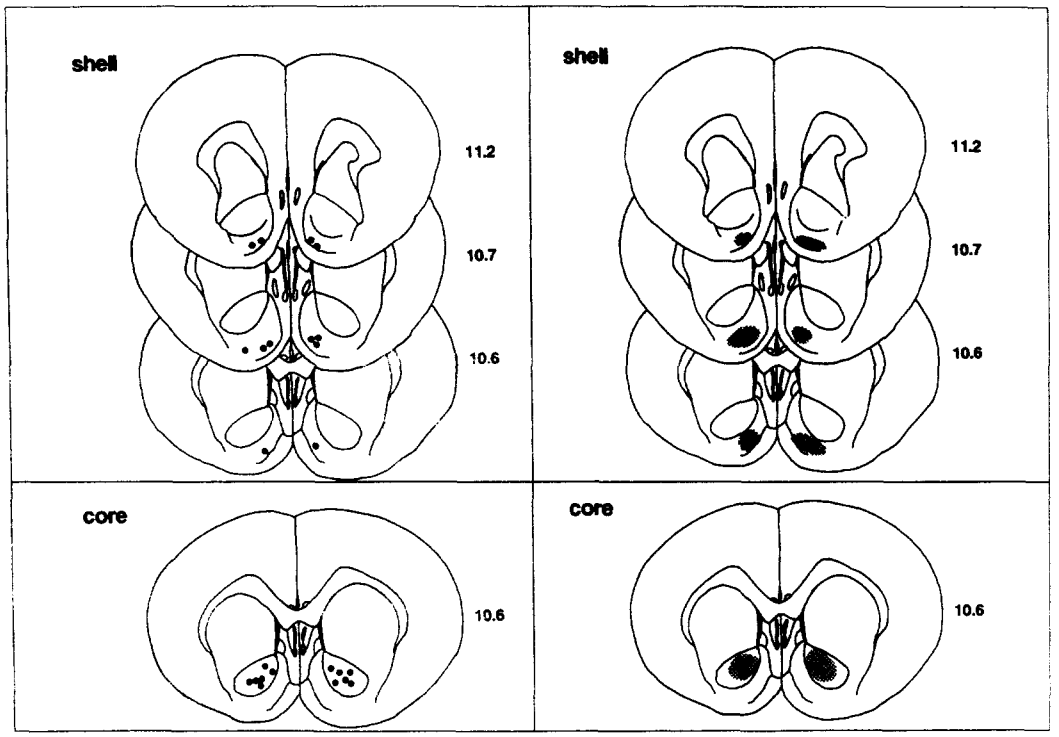

Fig. 1. Right side: the regions in which all injection sites were located for the shell (upper part) and the core (lower part). Left side: all sites found after injections of the mixture of SKF 82958 and quinpirole into the shell (upper part) and the core (lower part).

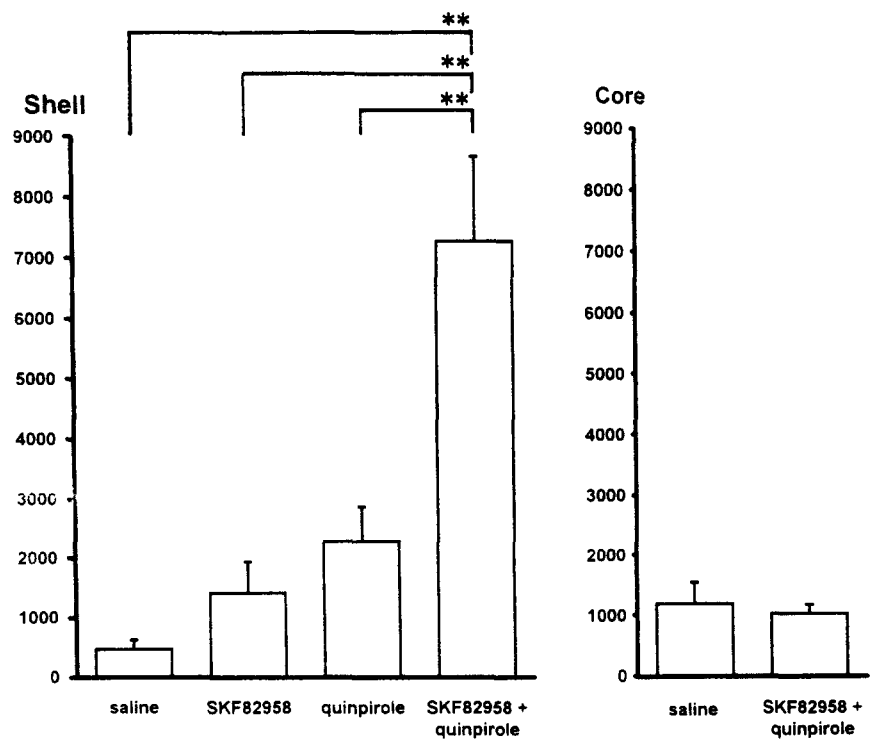

Fig. 2. The effect of injections of saline, 5 μg SKF 82958, 10 μg quinpirole and the mixture of 5 μg SKF 82958 and 10 μg quinpirole into the shell and the core of the nucleus accumbens (0.2 μl/side). The number of jaw movements observed during the period of 240 min after the injections (means ± S.E.M.) is given, ** $P < 0.05$.

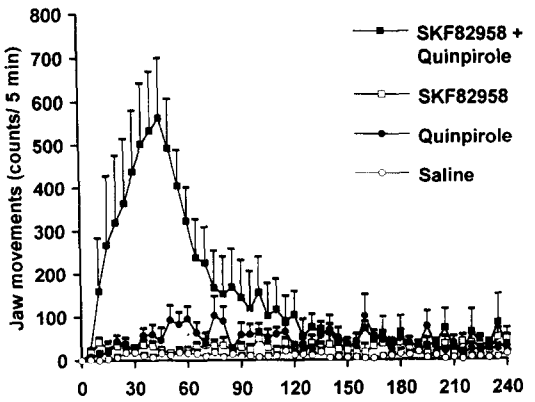

Fig. 3. The time-dependent effects of injections of saline, 5 μg SKF 82958, 10 μg quinpirole and the mixture of SKF 82958 and quinpirole into the shell of the nucleus accumbens (0.2 μl/side). The number of jaw movements observed per 5 min (means ± S.E.M.) is given.

ment produced a reduction in two of the six tested rats; the mean number of jaw movements in these two rats was 858 ± 84, whereas the mean number of jaw movements in the remaining four rats was 4851 ± 138. Histological analysis showed that the two effective sulpiride injections were placed in the ventromedial part of the shell (coordinates according to the atlas of Paxinos and Watson (1986): interaural plane: 10.7; bregma: 1.7; vertical: 2.3).

4. Discussion

The outcome of the present study confirms the earlier reported finding that the shell, but not the core, of the nucleus accumbens is involved in the control of oral behaviour, especially jaw movements (Bordi et al., 1989; Cools et al., 1993; Prinssen et al., 1994): the combined administration of SKF 82985 and quinpirole was only effective when injected into the shell, but not the core, of the nucleus accumbens. The finding that especially the shell of the nucleus accumbens is involved in oral behaviour is understandable in view of the fact that the shell projects to a part of the ventral pallidum, that is known to be involved in oral behaviour (Spooren et al., 1989).

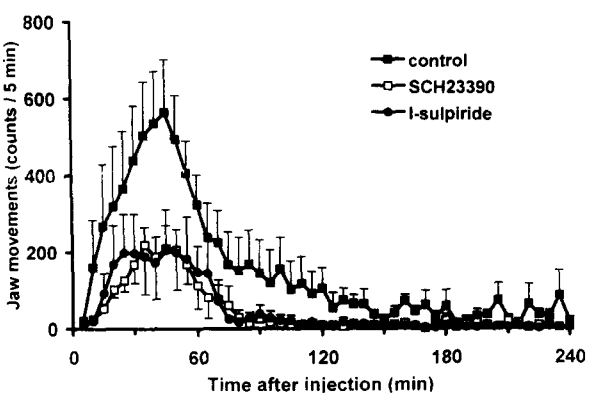

Fig. 4. The effect of 0.5 μg SCH 23390 (0.2 μl per side), given 10 min prior to the mixture of 5 μg SKF 82958 and 10 μg quinpirole (open squares) and that of 25 μg (−)-sulpiride (0.5 μl per side), given 30 min prior to the same mixture (0.2 μl/side; closed circles): all injections were made into the shell of the nucleus accumbens. The number of jaw movements observed per 5 min (means ± S.E.M.) is given. Control = effect of the mixture of SKF 82958 and quinpirole (closed squares).

Although the full dopamine D_1 receptor agonist SKF 82958 has some anomalous properties in certain assays (Murray and Waddington, 1989; Mottola et al., 1992; O'Boyle et al., 1989), both the dopamine D_1 receptor agonist SKF 38393 which lacks these anomalous properties, and the dopamine D_1 agonist SKF 82958 produced similar effects when combined with quinpirole (Koshikawa et al., 1990; Prinssen et al., 1992; Koene et al., 1993). This together with the finding that the dopamine D_1 receptor antagonist SCH 23390 antagonized the effects of the SKF 82958-quinpirole cocktail provides evidence that dopamine D_1 receptors were involved. Quinpirole, however, is a dopamine receptor agonist that has a high affinity not only for dopamine D_2 receptors (Stoof and Kebabian, 1981), but also for dopamine D_3 receptors (Sokoloff et al., 1990). For that reason, we analyzed the ability of the highly selective dopamine D_2 receptor antagonist (−)-sulpiride (Spano et al., 1979) to inhibit the effects seen. As shown in Fig. 4, (−)-sulpiride did inhibit the effects. As mentioned in the Results section, (−)-sulpiride was effective in all rats when injected in a volume of 0.5 μl, but effective only in two out of six rats when injected in a volume of 0.2 μl. Since the latter injections were located in a circumscribed part of the shell, these data suggest that (−)-sulpiride did not really diffuse, implying that this drug is an extremely useful tool in studies on the delineation of critical regions in the brain. Anyhow, the observation that (−)-sulpiride inhibited the effects of SKF 82985 and quinpirole provides evidence that dopamine D_2 receptors were involved as well. It has to be noted that this does not mean that dopamine D_3 receptors play no role in this respect: future studies are necessary to establish their role in this respect.

Previously, we and others have reported that dopamine D_1 receptor agonists and dopamine D_2 receptor agonists have similar or opposite effects which are additive or antagonistic depending on the behaviour studied (Koene et al., 1993; Waddington, 1993). Concerning jaw movements elicited by intra-accumbens injections of these agents, it has been reported that administration of just one of these agonists being either SKF 38393 or quinpirole has no significant effect on jaw movements, excluding thereby the possibility to study possible counteracting effects in this respect.

Thus, the present data show that combined stimulation of dopamine D_1 and D_2 receptors produces additive effects on jaw movements when injected into the shell of the nucleus accumbens.

The present data clearly show that the differences in the dopamine neurotransmission between the shell and the core of the nucleus accumbens which are mentioned in the Introduction section have direct consequences for the function of dopamine in these two domains: dopamine D_1 and D_2 receptors in the shell, but not in the core, modulate the display of jaw movements in the rat. To what extent these receptors also mediate the reward reinforcing effects of psychostimulants remains to be investigated.

In sum, the present study provides the first piece of evidence that the dopamine D_1 and D_2 receptors in the shell, but not the core, are involved in the control of jaw movements in the rat.

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