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Behavioural responses to the selective D_1-dopamine receptor agonist R-SK&F 38393 and the selective D_2-agonist RU 24213 in young compared with aged rats

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1 In aged male Sprague-Dawley rats (22 months) with a selective loss of D_2- but not of D_1-dopamine receptors, stereotyped behaviour induced by 0.5 mg kg^{-1} apomorphine was increased and prolonged in comparison with young (4 month) counterparts. This suggested a pharmacokinetic effect rather than a pharmacodynamic change.

2 The syndrome of non-stereotyped behavioural responses to the selective D_1-agonist R-SK&F 38393, 1.25–20.0 mg kg^{-1}, was unchanged in aged vs young animals, but the topography of individual behaviours constituting this overall syndrome was altered with aging.

3 Neither the overall syndrome of low intensity stereotyped behaviour nor the topography of individual behaviours induced by the selective D_2-agonist RU 24213, 1.25–20.0 mg kg^{-1}, were altered in aged vs young animals.

4 Loss of D_2- but not D_1-receptors with aging was therefore found to be associated with no change in responsivity to a D_2-receptor agonist. The decreased intense grooming and increased vacuous chewing responses to the D_1-agonist with aging parallel the previously demonstrated effects of selective D_2-antagonists on these D_1-stimulated behaviours.

5 It is suggested that age-related decline in D_2-receptor activity may have greater functional consequences in relation to D_1-:D_2-interactions than in simply influencing responsivity to a D_2-agonist. Such interactive effects should be taken into account when considering the pathophysiology and treatment of age-related extrapyramidal movement disorders.

Introduction

Numerous studies have now documented a reduction in the number of striatal dopamine receptors with increasing age in rodent, primate and human brain. While the density of receptors of the D_2-sub-type (Kebabian & Calne, 1979) is reliably found to be reduced in the aged brain, there is less consistent evidence on whether similar changes in D_1-receptors occur (for reviews, see Roth & Hess, 1982; Waddington *et al.*, 1985; Morgan *et al.*, 1987).

In probing for any functional significance to such age-related loss of dopamine receptors, several investigators have challenged aged rodents with dopamine receptor agonists and have examined their behavioural responsivity in comparison with young counterparts. While overall stereotypy responses to the classical agonist apomorphine are enhanced with aging (Smith *et al.*, 1978; Randall *et al.*, 1981), recent data indicate a prominent influence of altered pharmacokinetics, such that higher plasma and brain levels of apomorphine are evident in aged animals

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(Watanabe *et al.*, 1982; Campbell *et al.*, 1984). Additionally, apomorphine is a non-selective agonist at both D_1- and D_2-receptors (Kebabian & Calne, 1979; Seeman, 1980). These characteristics make apomorphine a poor tool for clarifying functional correlates of age-related changes in the parameters of dopamine receptor sub-types at the behavioural level, and have contributed to inconsistencies in the literature on this issue.

This study uses agents that act selectively on D_1- or D_2-receptors, and which are primarily eliminated via simple conjugation reactions rather than undergoing complex metabolic transformation. The racemic compound and particularly the pharmacologically active R-enantiomer of the selective D_1-agonist SK&F 38393 (Setler *et al.*, 1978; Weinstock *et al.*, 1985) induce a discontinuous, non-stereotyped activation of behaviour, characterized by episodes of a prominent grooming response interpolated among episodes of sniffing with some locomotion and rearing (Molloy & Waddington, 1984; 1987; Starr & Starr, 1986). The selective D_2-receptor agonist RU 24213 (Euvrard *et al.*, 1979) induces 'low-intensity stereotypy' consisting of bursts of continuous sniffing and locomotion (Pugh *et al.*, 1985). We have studied behavioural responses to their peripheral administration in young vs aged rats.

Methods

Animals

Male Sprague-Dawley rats aged 4 months (275–450 g, young adult) or 22–23 months (450–775 g, aged) were obtained from the Wolfson Institute for Gerontology, Hull, U.K.

Assessment of behavioural responses to R-SK&F 38393

As previously described in detail (Molloy & Waddington, 1984; 1987a), animals were placed individually in large perspex cages and left undisturbed for a habituation period of 2.5 h. Immediately before and at intervals after challenge with drug or vehicle, animals were assessed by a rapid time-sampling behavioural check list technique. For this procedure, each rat was observed for 5 s periods at 1 min intervals over 5 consecutive min using a behavioural check list. This allowed the presence or absence of the following typical individual behaviours (occurring alone or in combination) to be determined; sniffing, locomotion, rearing, grooming; an additional category of intense grooming was used to describe a characteristic pattern where grooming of the snout with the forepaws was followed by vigorous grooming of the hind flank with the snout. Atypical behaviours are described individually in the text. After assessment by the behavioural check list, animals were rated on a conventional 0–6 stereotypy scale. This cycle of observations was then repeated at 10 min intervals.

From this rapid time-sampling behavioural check list procedure, the number of counts of individual behaviours were determined as the number of 5 s observation 'windows' in which a given behaviour or any one of several behaviours was evident (up to the maximum of five for each time point); these counts could then be summed over several time points, as indicated. Behavioural counts are indicated as means ± s.e.mean, and were analysed by the Mann-Whitney U test.

Assessment of behavioural responses to RU 24213 and apomorphine

As previously described in detail (Molloy & Waddington, 1984; Pugh *et al.*, 1985), animals were placed individually in large perspex cages and left undisturbed for a habituation period of 2.5 h. Immediately before and at intervals after challenge with drug or vehicle, each animal was observed for a 1 min period. It was rated by the above stereotypy scale, and the behavioural check list used to specify the presence or absence of the individual elements of behaviour contributing to the overall syndrome evident. This cycle of observations was then repeated at 10 min intervals.

Stereotypy scores are expressed as means ± s.e.mean, and were analysed by the Mann-Whitney U test. The presence or absence of individual elements of behaviour is expressed as their percentage prevalence within each group, which was analysed by the Fisher exact probability test.

Drugs

R-SK&F 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine hydrochloride; Smith Kline & French) and RU 24213 (N-*n*-propyl-N-phenylethyl-*p*-3-hydroxyphenyl-ethylamine hydrochloride; Roussel-UCLAF) were dissolved in distilled water. Apomorphine hydrochloride (Sigma) was dissolved in distilled water containing 0.1% sodium metabisulphite as antioxidant. All injections were given s.c. into the flank, with control animals receiving s.c. injections of vehicle alone. Young and aged animals were run in parallel within each test session. Behavioural assessments were made by an observer unaware of the treatment given to each animal.

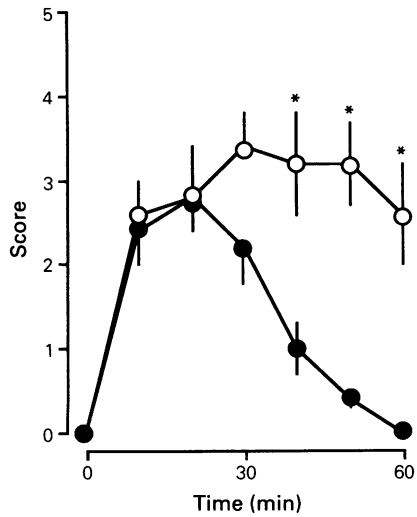

Figure 1 Stereotypy scores in young (●) and aged (○) animals against time (min) after challenge with apomorphine 0.5 mg kg^{-1}. Data are means with s.e.mean shown by vertical lines, $n = 5$ per group. * $P < 0.05$ vs young animals.

Results

Responses to apomorphine

Stereotypy scores following treatment with 0.5 mg kg^{-1} apomorphine reached their peak at 20 min in young animals; they declined steadily thereafter and no response was evident at 60 min (Figure 1). In aged animals, stereotypy scores tended to attain values higher than the peak score of their young counterparts, and were sustained for a more prolonged period ($P < 0.05$).

Responses to R-SK&F 38393

No stereotyped behaviour was induced by R-SK&F 38393. Peak scores were as follows: young animals, vehicle 0.9 ± 0.3, 20 mg kg^{-1} R-SK&F 38393 1.2 ± 0.2 ($n = 8$–9); aged animals, vehicle 0.7 ± 0.2, 20 mg kg^{-1} R-SK&F 38393 1.4 ± 0.2 ($n = 8$–9).

Though they induced no stereotypy, vehicle injections increased slightly the initial number of observation windows in which one or more of the typical behaviours of sniffing, grooming of any type, locomotion and rearing was displayed in a non-stereotyped manner (Figure 2). There was a greater activating effect of vehicle injections in aged than in young animals at the 10 min and 60 min points ($P < 0.05$). These baseline levels of behavioural counts were dose-dependently increased by 1.25–20.0 mg kg^{-1} R-SK&F 38393. Though responses to R-SK&F 38393 appeared somewhat blunted in aged animals, there were no significant differences in either peak level or overall time-course of this composite response between young and aged groups at any dose.

Cumulative behavioural counts for the individual behaviours of sniffing and intense grooming, summed over the 20–50 min time points of peak drug effect relative to vehicle controls, revealed them to be differentially influenced. There was an indistinguishable ($P < 0.01$) dose-dependent promotion of sniffing by 1.25–20.0 mg kg^{-1} R-SK&F 38393 in both young and aged animals (Table 1), while a dose-dependent induction of intense grooming was evident only in the young group ($P < 0.01$); in their aged counterparts, the combination of tendencies for the vehicle baseline to be higher and for the drug response to be lower resulted in no significant dose-response relationship. An atypical accessory behaviour of vacuous chewing emerged in aged animals. These masticatory jaw movements, but not directed onto any physical material, were negligibly induced in young animals but were dose-dependently induced in the aged group ($P < 0.05$).

Responses to RU 24213

'Low intensity stereotypy', consisting of bursts of continuous sniffing and locomotion, was dose-dependently induced by 1.25–20.0 mg kg^{-1} RU 24213 (Figure 3).

Table 1 Counts for the individual behaviours of sniffing (Sn), intense grooming (Gr_i) and vacuous chewing (VCh) in young and aged animals after challenge with the D_1-receptor agonist, R-SK&F 38393

Drug (mg kg^{-1})		Sn		Gr_i		VCh	
		young	aged	young	aged	young	aged
Vehicle	—	2.9 ± 0.9	3.3 ± 1.0	0.1 ± 0.1	1.3 ± 0.6	0.2 ± 0.1	0.9 ± 0.4
R-SK&F 38393	1.25	5.8 ± 1.6	5.0 ± 1.5	2.4 ± 0.4**	1.6 ± 0.5	1.1 ± 0.5	0.4 ± 0.2
	5.0	8.1 ± 1.3**	6.9 ± 0.8*	4.5 ± 0.7**	2.9 ± 0.6	1.0 ± 0.3	1.3 ± 0.3
	20.0	11.3 ± 1.3**	12.3 ± 1.8**	4.3 ± 1.0**	2.7 ± 0.3	0.8 ± 0.4	2.6 ± 0.6*

Values are means ± s.e.mean of counts summed over the 20–50 min periods for each of the groups of Figure 2 ($n = 8$–9). Significant differences from vehicle-treated animals: ** $P < 0.01$; * $P < 0.05$.

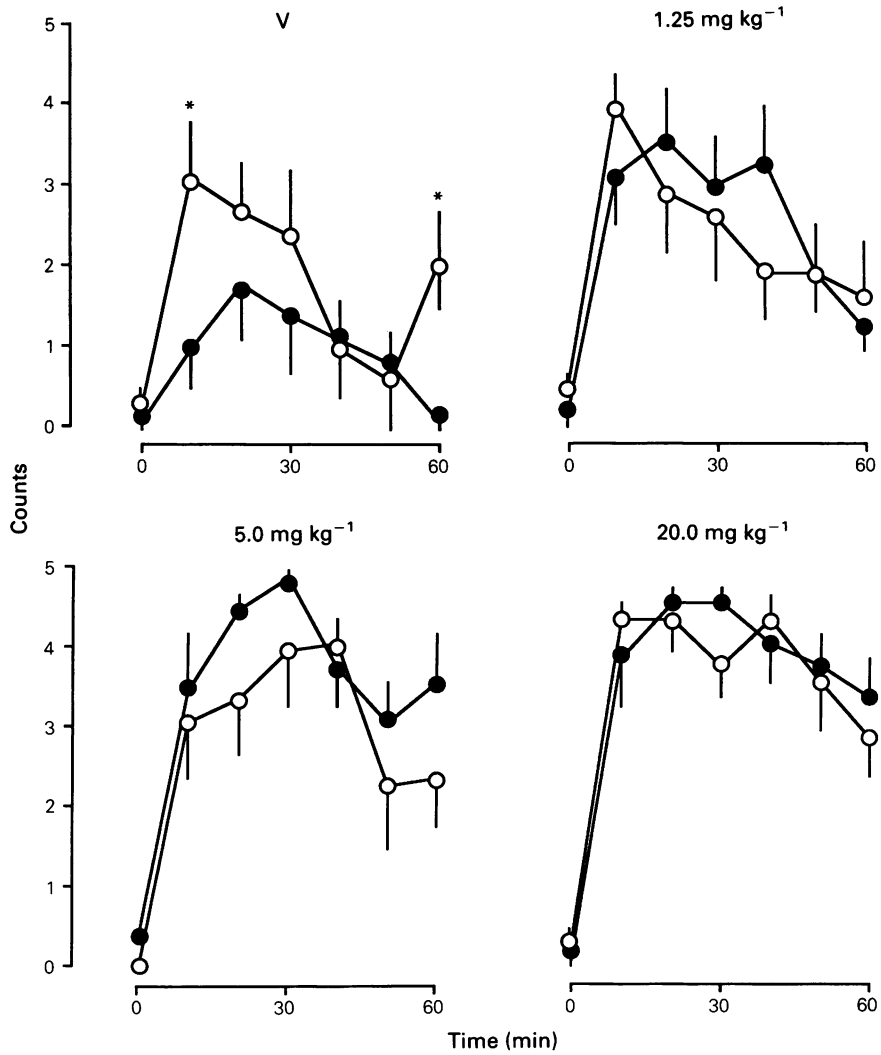

Figure 2 Counts for any typical behaviour in young (●) and aged (○) animals against time (min) after challenge with vehicle (V) or 1.25–20.0 mg kg^{-1} R-SK&F 38393. Data are means with s.e.mean shown by vertical lines, $n = 8$–9 per group. * $P < 0.05$ vs young animals.

Following 1.25 mg kg^{-1} RU 24213, the peak score evident in young animals was significantly delayed ($P < 0.05$) in their aged counterparts. However, the magnitude of this peak response was not significantly altered in the aged group. There were no significant differences either in peak scores or times to peak score in response to 5.0 and 20.0 mg kg^{-1} RU 24213 between young and aged animals.

Prevalence of the individual behaviours of sniffing, locomotion and rearing within the overall syndrome of behaviour was increased in a dose-dependent manner by RU 24213 and was indistinguishable between young and aged animals at each dose (Table 2).

Discussion

Loss of D_2-receptors with aging (see Introduction) has been confirmed in living man by positron emission tomography (Wong *et al.*, 1984). In rats identical with those used in the present study, we have reported (O'Boyle & Waddington, 1984; 1986) a 26% reduction in striatal D_2-receptor density with

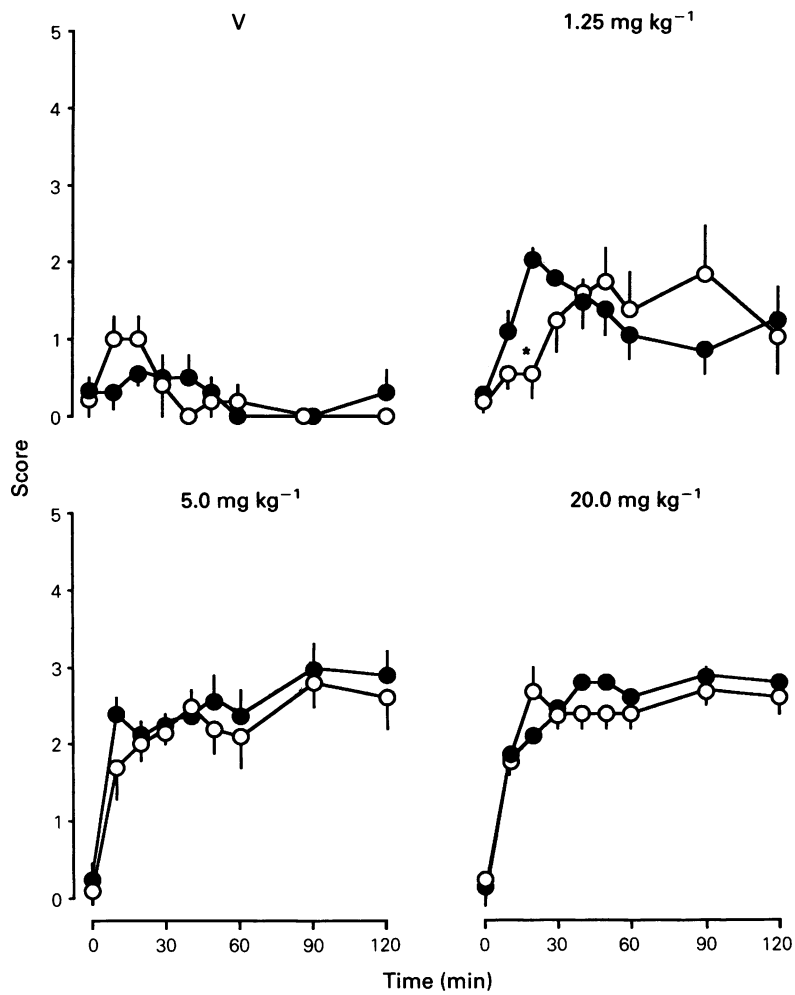

Figure 3 Stereotypy scores in young (●) and aged (○) animals against time (min) after challenge with vehicle (V) or 1.25–20.0 mg kg^{-1} RU 24213. Data are means with s.e.mean shown by vertical lines, $n = 5$–14 per group. * $P < 0.05$ vs young animals.

Table 2 Prevalences of the individual behaviours of sniffing (Sn), locomotion (L) and rearing (R) in young and aged animals after challenge with the D_2-receptor agonist RU 24213

		Sn		L		R	
Drug (mg kg^{-1})		young	aged	young	aged	young	aged
Vehicle	—	0%	0%	0%	0%	0%	0%
RU 24213	1.25	64%*	55%	27%	18%	18%	18%
	5.0	93%**	77%**	71%	38%	36%	15%
	20.0	100%**	100%**	100%**	89%*	42%	56%

Values are percentage prevalences for each of the groups of Figure 3 ($n = 5$–14), at 60 min after drug challenge. Significant differences from vehicle-treated animals: ** $P < 0.01$; * $P < 0.05$.

no change in affinity, between the same ages (4 and 22 months) compared here behaviourally.

Increased stereotypy responses to apomorphine in aged rodents appear to have a basis in higher drug concentrations in plasma and brain (Watanabe *et al.*, 1982; Campbell *et al.*, 1984). In male Sprague-Dawley rats, as used here, there is a lack of parallelism between changes in body weight and in response to or tissue level of apomorphine (for detailed analysis, see Campbell *et al.*, 1984); thus, the greater body weight of aged animals does not appear to account for the altered response to a drug given on a $mg\,kg^{-1}$ basis. Several processes involved in the complex pharmacokinetic profile of apomorphine (Di Chiara & Gessa, 1978; Smith *et al.*, 1979) are known to be impaired in the aged male rat (Schmucker, 1985; Kitani, 1986).

The diphenethylamine derivative RU 24213 is a selective D_2-receptor agonist that appears to be eliminated predominantly by simple conjugation as the glucuronide (Euvrard *et al.*, 1979; unpublished data kindly provided by Roussel-UCLAF). Conjugation may be less influenced by aging than other pathways of drug metabolism in the male rat (Schmucker, 1985; Kitani, 1986). At the lowest dose of RU 24213 used, the peak response evident in young animals was significantly delayed in their aged counterparts; however, a response of similar peak was ultimately attained. At higher doses, the onset, peak, and topography of the sniffing and locomotor syndrome were indistinguishable between young and aged groups. Clearly, measurement of drug levels would be needed to establish the point and to exclude any interactions between behavioural responsivity and age-related changes in one or more phases of drug metabolism/excretion. However, our *in vivo* results are complementary to the *in vitro* studies of Missale *et al.* (1987). These authors reported that the inhibition of striatal adenylate cyclase by D_2-receptor stimulation was unchanged between male Sprague-Dawley rats of 3, 14 and 24 months despite an age-related loss of D_2-receptors.

In rodents, striatal D_1-receptors have been reported to be unaltered (O'Boyle & Waddington, 1984; Henry *et al.*, 1986; Morgan *et al.*, 1987) or reduced (Henry *et al.*, 1986; Giorgi *et al.*, 1987). In rats similar to those used in the present study, we have reported (O'Boyle & Waddington, 1984) no change in either D_1-receptor density or affinity between the same ages (4 and 22 months) compared here behaviourally.

The introduction of D_1-receptor agents, especially the selective antagonists SCH 23390 and R-SK&F 83566, has indicated a prominent role for the D_1-receptor in the regulation of behaviour (for reviews, see Waddington, 1986; Breese & Creese, 1986; Waddington & O'Boyle, 1987). We have reported in the whole animal characteristic non-stereotyped behavioural responses to the selective D_1-receptor agonist SK&F 38393, and particularly to its active R-enantiomer (Molloy & Waddington, 1984; 1987a). The required assessment procedure is of sufficient sensitivity to detect brief activating effects of vehicle injections alone (Molloy & Waddington, 1987a), and this action was more evident in aged than in young animals. After drug challenge, we could detect no major alterations with aging in either the peak or the time-course of this syndrome induced by R-SK&F 38393, though there was a suggestion of some blunting of responsivity. This suggested the absence of any major age-related changes in the pharmacokinetics of SK&F 38393, which is also eliminated from the rat predominantly via a simple conjugation to the glucuronide (Weinstock *et al.*, 1985). Again, measurement of drug levels would be required to establish the point.

However, there were opposite changes with aging in the grooming and vacuous chewing behaviours constituting the overall pattern of response to R-SK&F 38393. How are we to resolve the apparent paradox that in aged animals with a selective loss of D_2- but not D_1-receptors, responsivity to a D_2-agonist appears unchanged while the topography of behaviours induced by a D_1-agonist is altered? If there are spare receptors, some loss may not influence drug action; also, changes in second-messenger function may play a role. Additionally, age-dependent alterations in non-dopaminergic systems or in the selectivity of action of these drugs cannot be excluded. However, we suggest some involvement of the functional interactions between D_1- and D_2-systems, which have been proposed (Molloy & Waddington, 1984; Christensen *et al.*, 1984). In the whole animal it appears that D_1-tone can exert a prominent facilitatory role in the regulation of the expression of typical D_2-agonist-induced behaviours, and *vice-versa*, with the full expression of dopaminergic behaviour requiring concurrent stimulation of both receptor sub-types (Molloy *et al.*, 1986; Mashurano & Waddington, 1986; Braun & Chase, 1986; Waddington, 1986; Arnt *et al.*, 1987).

While all responses to R-SK&F 38393 are sensitive to antagonism by the selective D_1-receptor blockers SCH 23390 and R-SK&F 83566, the effects of the selective D_2-receptor antagonist metoclopramide are complex; behavioural counts for sniffing are not altered, while those for intense grooming are significantly attenuated by such selective D_2-blockade (Waddington *et al.*, 1986; Molloy & Waddington, 1987b). It is this same profile, that of unaltered sniffing and attenuation of intense grooming which is evident in our aged animals with a selective loss of D_2-receptors. Conversely, an atypical response to SK&F 38393, vacuous chewing, is

potentiated in the presence of a D_2-receptor antagonist (Rosengarten *et al.*, 1983; 1986). It is this same profile, that of enhanced vacuous chewing, which is evident in our aged rats. That intense grooming and vacuous chewing responses to R-SK&F 38393 may be influenced in opposite directions by changes in D_2-receptor activity with aging has a parallel in how the direction of D_1-:D_2-interactions in electrophysiological studies (Carlson *et al.*, 1986; 1987) is opposite to that evident at the level of striatal neurochemistry (Saller & Salama, 1986; Consolo *et al.*, 1987). Thus the typical grooming response and the atypical vacuous chewing response appear to involve distinct neural mechanisms activated by D_1-receptor stimulation, each with a different pattern of interaction with D_2-systems (Waddington & O'Boyle, 1987) and differentially influenced by aging.

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