Cannabinoids Cause Central Sympathoexcitation and Bradycardia in Rabbits¹

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ABSTRACT
Systemically administered cannabinoids elicit marked cardiovascular effects, and the role of the central and the peripheral nervous system in these effects is not clarified. The aim of this study was to characterize the actions of cannabinoids on cardiovascular regulatory centers in conscious rabbits. A catheter for administration of drugs into the cisterna cerebellomedullaris and an electrode for recording renal sympathetic nerve activity were implanted under halothane anesthesia. Experiments were carried out later in conscious animals. Two cannabinoid receptor agonists were injected intracisternally: the aminoalkylindole WIN55212-2 (0.1, 1, and 10 µg kg⁻¹) and the bicyclic Δ⁹-tetrahydrocannabinol analog CP55940 (0.1, 1, and 10 µg kg⁻¹). WIN55212-2 and CP55940 dose dependently increased renal sympathetic nerve activity and the plasma noradrenaline concentration and also lowered the heart rate. The highest doses of WIN55212-2 and CP55940 increased blood pressure. In contrast, intracisternal injection of WIN55212-3 (0.1, 1, and 10 µg kg⁻¹), an enantiomer of WIN55212-2 with very low affinity for cannabinoid binding sites, had no effects. The CB₁ cannabinoid receptor antagonist SR141716A (0.5 mg kg⁻¹, i.v.) attenuated the effects of intracisternally administered WIN55212-2 (0.1, 1, and 10 µg kg⁻¹). The results indicate that cannabinoids, acting directly on cardiovascular regulatory centers, elicit sympathoactivation and bradycardia. These effects were likely mediated by CB₁ cannabinoid receptors, because they were elicited by two cannabinoid agonists belonging to different chemical classes (WIN55212-2 and CP55940), but not by the inactive enantiomer WIN55212-3, and because they were attenuated by the CB₁ cannabinoid receptor antagonist SR141716A.

Several effects of natural and synthetic cannabinoid agonists are well characterized in humans and experimental animals, e.g., euphoria, analgesia, change in locomotion, catalepsy, temperature reduction, and memory disturbance (for review, see Dewey, 1986; Compton et al., 1995a; Howlett, 1995a; Compton et al., 1996; Pertwee, 1997).

In contrast, although cannabinoids elicit prominent cardiovascular effects, relatively little is known on the mechanism of these effects (for review, see Dewey, 1986; Compton et al., 1996; Wagner et al., 1998). In conscious humans, cardiovascular responses to acute administration of Δ⁹-tetrahydrocannabinol include a marked tachycardia and a small increase in blood pressure (Benowitz et al., 1979; Huestis et al., 1992). In anesthetized animals, systemically administered cannabinoids generally lower blood pressure and heart rate [e.g., rat (Vidrio et al., 1996; Lake et al., 1997), dog (Jandhyala and Hamed, 1978; Stark and Dews, 1980)]. In most of these studies, only blood pressure and heart rate were measured, and the location of the effects to peripheral and central components of the cardiovascular regulatory system was not possible.

Only a few experiments were carried out to characterize the effects of cannabinoids on cardiovascular regulatory centers. In previous studies in anesthetized animals, centrally administered Δ⁹-tetrahydrocannabinol caused central sympathoinhibition and enhancement of cardiac vagal tone (Cavero et al., 1973a,b; Vollmer et al., 1974), whereas systemically administered anandamide had no central cardiovascular effect (Varga et al., 1996). In a recent study (Niederhofer and Szabo, 1999), we injected the synthetic cannabinoid receptor agonist WIN55212-2 into the cisterna cerebellomedullaris of conscious rabbits to observe its effects on cardiovascular centers in the medulla oblongata. WIN55212-2 increased the plasma noradrenaline concentration, indicating central sympathoexcitation; consequently, blood pressure increased. WIN55212-2 also caused marked bradycardia. All these studies did not allow a conclusion to be

ABBREVIATIONS: PRE, average of initial values (before administration of cannabinoid agonists); i.c., intracisternal.

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made on the involvement of specific cannabinoid receptors in the central cardiovascular effects of cannabinoids.

In these experiments, we further analyzed the effects of cannabinoids on medullary cardiovascular centers in conscious rabbits. The first aim was to study whether specific cannabinoid receptors are involved in the effects of intracisternally given cannabinoid agonists. To this end, the effects of WIN55212-2 were compared with the effects of WIN55212-3 and CP55940. WIN55212-3 is an enantiomer of WIN55212, and its affinity for cannabinoid binding sites is very low (Kuster et al., 1993; Pertwee, 1997). The chemical structure of CP55940 (a bicyclic compound structurally resembling Δ9-tetrahydrocannabinol) differs markedly from that of WIN55212-2 (an aminooalkylindole) (Pertwee, 1997). The interaction between WIN55212-2 and the CB1 cannabinoid receptor antagonist SR141716A (Rinaldi-Carmona et al., 1994; Pertwee, 1997) was also studied. The second aim was to observe centrally elicited changes in sympathetic tone directly; to this end, sympathetic nerve activity was recorded.

**Materials and Methods**

Experiments were carried out on 21 rabbits of a local breed (derived from Deutscher Riesenscheck, obtained from Ketterer, Reute, Germany). Rabbits were of both sexes and weighed 1.8 to 3.3 kg. Experiments were carried out on 21 rabbits of a local breed (derived from Deutscher Riesenscheck, obtained from Ketterer, Reute, Germany). Rabbits were of both sexes and weighed 1.8 to 3.3 kg. In a first operation, a catheter was implanted into the cisterna cerebellomedullaris under halothane anesthesia (1.5–4%) in spontaneously breathing rabbits (for details, see Szabo et al., 1993). Briefly, a polyethylene catheter (i.d., 0.28 mm; o.d., 0.61 mm; length, 25 cm) was inserted 8 mm into the cisterna cerebellomedullaris through a hole in the atlanto-occipital membrane. The free end of the catheter was tunneled to an incision in the neck, and the wounds were sutured.

A second operation was performed after 2 weeks of recovery. Under halothane anesthesia (1.5–4%) in spontaneously breathing rabbits, an electrode was implanted for recording activity of postganglionic renal sympathetic nerves (for details, see Szabo et al., 1993). Briefly, the left kidney was approached retroperitoneally, and two sympathetic nerve trunks accompanying the renal artery were dissected free and slipped into the spirals of a stainless steel bipolar electrode. The nerves and the electrode were embedded in silicone gel. The free end of the electrode was tunneled to an incision in the neck, and the wounds were sutured.

**Experiments in Conscious Rabbits.** The first experiment in the conscious animal was carried out 3 to 4 days after implantation of the renal nerve electrode. Two to three experiments were carried out on one rabbit at 3- to 4-day intervals. No animal received a given treatment twice. After the last experiment, the animals were sacrificed by an overdose of pentobarbitone.

On the day experiments were performed in conscious animals, the central ear artery was cannulated under local anesthesia for recording arterial blood pressure and heart rate and for blood sampling. Arterial pressure was recorded with a Statham P23Db transducer coupled to a bridge amplifier (Hugo Sachs Elektronik, Hugstetten, Germany); heart rate was calculated from the pulsating blood pressure signal by an integrator (Hugo Sachs Elektronik). A marginal ear vein was also cannulated; this served for reinjection of erythrocytes (resuspended in saline) of blood samples and, in some experiments, for administration of the CB1 cannabinoid receptor antagonist SR141716A. Also under local anesthesia, the intracisternal (i.c.) catheter and electrode leads were recovered from under the skin.

The plasma noradrenaline concentration was determined as previously described (Szabo and Schultheiss, 1990). Briefly, 2 ml blood samples were obtained, and plasma catecholamines were determined by alumina chromatography followed by HPLC and electrochemical detection.

**Protocol and Statistics.** Parameters were first determined 45 min (t = 0 min) after recovery of the catheter and electrode leads. Either solvent (SOL) (25 μL kg⁻¹) or increasing doses of WIN55212-2 (0.1, 1, and 10 μg kg⁻¹), WIN55212-3 (0.1, 1, and 10 μg kg⁻¹), or CP55940 (0.1, 1, and 10 μg kg⁻¹) were injected i.c. at t = 19, 37, and 55 min (for protocol, see Fig. 1). In experiments with the CB1 cannabinoid receptor antagonist SR141716A, the antagonist (0.5 mg kg⁻¹) was injected i.v. at t = −10 min; WIN55212-2 (0.1, 1, and 10 μg kg⁻¹) was injected i.c. at t = 19, 37, and 55 min. In all experiments, blood pressure and heart rate (and in most groups also renal sympathetic nerve activity) were read every 2 min from t = 0 to 68 min. Blood was sampled at t = 0, 14, 32, 50, and 68 min for the determination of the plasma noradrenaline concentration. In each experiment, values measured at t = 0 and 14 min were averaged to yield the average of initial values before administration of cannabinoid agonists.

![Fig. 1. Effect of WIN55212-2 (WIN-2) on mean arterial pressure (MAP), heart rate (HR), renal sympathetic nerve activity (RSNA), and plasma noradrenaline concentration (PL-NA) in a conscious rabbit (original tracings). WIN55212-2 (0.1, 1, 10 μg kg⁻¹) was injected i.c., as indicated by the arrows.](image-url)
agonists (PRE values), and all values were expressed as percentages of PRE.

Data were analyzed with the SPSS for Windows statistical program (version 8.0.0; SPSS, Chicago, IL). Means ± S.E. of n experiments are given throughout. Two-way ANOVA coupled with Scheffe’s test was used to identify significant differences; P < .05 was taken as the limit of statistical significance, and only this level is indicated even if P was <.01 or <.001.

Drugs. Drugs were obtained from the following sources: (−)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol (CP55940) from Pfizer (Groton, CT); 2-hydroxypropyl-β-cyclodextrin from Fluka (Neu-Ulm, Germany); N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-carboxamide (SR141716A) from Sanofi Recherche (Montpellier, France); R(1)[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone mesylate (WIN55212-2) and S(2)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone mesylate (WIN55212-3) from Research Biochemicals International (Köln, Germany).

WIN55212-2, WIN55212-3, and CP55940 were dissolved and further diluted in a 7.5% 2-hydroxypropyl-β-cyclodextrin solution (w/v in distilled water); they were injected i.c. in a volume of 25 μl kg⁻¹ within 1 min. SR141716A was dissolved in a vehicle containing ethanol/Emulphor (Rhone-Poulenc, Cranberry, NJ)/saline (1:1:18, v/v); it was injected i.v. in a volume of 0.5 ml kg⁻¹. Doses refer to the salts.

Results

Baseline Parameters (PRE Values). After an initial stabilization period, baseline parameters were determined twice (at t = 0 and 14 min), and the values were averaged to obtain the PRE values. Mean PRE values in animals without pretreatment were: mean arterial pressure, 70 ± 1 mm Hg (n = 32); heart rate, 211 ± 6 min⁻¹ (n = 32); renal sympathetic nerve activity, 33 ± 3 impulses s⁻¹ (n = 24); and plasma noradrenaline concentration, 237 ± 30 pg ml⁻¹ (n = 32). Similar values were obtained in previous studies using similar preparations (Szabo et al., 1993, 1995; Niederhoffer and Szabo, 1999). For further evaluation, values in any given experiment were expressed as percentages of PRE.

Control Experiments. Injection of the solvent (three times 25 μl kg⁻¹) into the cisterna cerebellomedullaris caused no change in mean arterial pressure, heart rate, renal sympathetic nerve activity, or the plasma noradrenaline concentration (Fig. 2).

Effects of WIN55212-2 and WIN55212-3. The effects of the aminoalkylindole cannabinoid agonist WIN55212-2 are shown in Fig. 1 (original tracings) and Fig. 2 (statistical evaluation). Three increasing doses (0.1, 1, and 10 μg kg⁻¹) were injected i.c. Blood pressure was not changed after the two lower doses but was significantly elevated after the highest dose. Central application of WIN55212-2 also elicited pronounced and dose-dependent bradycardia and dose-dependent increases in renal sympathetic nerve activity and plasma noradrenaline concentration. Effects of WIN55212-2 were compared with those of its inactive stereoisomer, WIN55212-3 (Fig. 2). Increasing doses of WIN55212-3 (0.1, 1, and 10 μg kg⁻¹; same doses as of WIN55212-2) had no effect on blood pressure, heart rate, and plasma noradrenaline concentration.

Effects of CP55940. The effects of the bicyclic analog of Δ²-tetrahydrocannabinol, CP55940, are shown in Fig. 3. Three increasing doses (0.1, 1, and 10 μg kg⁻¹) were injected i.c. as indicated by the arrows. Values are given as percentages of PRE. Means ± S.E. are from eight (SOL), eight (WIN-2), and eight (WIN-3) experiments. Differences from SOL: *P < .05. Renal sympathetic nerve activity was not determined in the group that received WIN-3.
The pattern of effects was very similar to that observed after administration of WIN55212-2. Thus, blood pressure increased significantly after the highest dose. CP55940 also elicited a dose-dependent bradycardia, a dose-dependent increase in renal sympathetic nerve firing, and a dose-dependent increase in plasma noradrenaline concentration.

Interaction between SR141716A and WIN55212-2.
The CB1 cannabinoid receptor antagonist SR141716A (0.5 mg kg\(^{-1}\)) was injected i.v. at \(t = -10\) min. It had no effect on the measured parameters. Thus, the PRE values of blood pressure, 70 ± 3 mm Hg (n = 8), heart rate, 223 ± 11 min\(^{-1}\) (n = 8), RSNA, 37 ± 5 impulses s\(^{-1}\) (n = 7), and plasma noradrenaline concentration, 209 ± 31 pg ml\(^{-1}\) (n = 8) did not significantly differ from the values measured in untreated animals (see above). However, pretreatment with SR141716A attenuated the effects of WIN55212-2 (Fig. 4). The highest dose of WIN55212-2 no longer significantly increased blood pressure in the SR141716A-pretreated animals. The bradycardia and the increase in sympathetic nerve activity observed after WIN55212-2 at 1 and 10 \(\mu\)g kg\(^{-1}\) were attenuated. The increase in plasma noradrenaline concentration observed after the highest dose of WIN55212-2 was also significantly antagonized by SR141716A.

Discussion
Administration of cannabinoids into the vicinity of cardiovascular centers in the medulla oblongata elicited two primary effects: sympathetic tone increased and heart rate decreased. The new finding of this study is that CB1 cannabinoid receptors are involved in these effects.

An increase in sympathetic tone was indicated by changes in two parameters, plasma noradrenaline concentration and RSNA. These results confirm our previous observation of a centrally elicited increase in plasma noradrenaline concentration after i.c. administration of a cannabinoid agonist (Niederhofer and Szabo, 1999). The increase in plasma noradrenaline concentration indicates enhanced noradrenaline release in many sympathetically innervated tissues; it is likely that vascular resistance increases in these tissues. This study demonstrates for the first time the central sympatoexcitatory effect of cannabinoids by direct electrical measurement of sympathetic nerve activity. We measured activity of renal sympathetic nerves because they reflect the function of many baroreceptor reflex-controlled sympathetic nerves. The functional consequence of the increased activity of renal sympathetic nerves is an increase in renal vascular resistance (Malpas et al., 1996).

Involvement of the central nervous system in the effects of cannabinoids on sympathetic tone and blood pressure has been seldom studied previously. Using the head cross-circulation experimental model in dogs, Cavero et al. (1973a) concluded that \(\Delta^9\)-tetrahydrocannabinol centrally depresses sympathetic tone. Blood pressure decreased in cats after injection of \(\Delta^9\)-tetrahydrocannabinol into the lateral cerebral ventricle, indicating central sympathoinhibition (Vollmer et al., 1974). In rats, the putative endogenous cannabinoid anandamide elicited hypotension through peripheral sites of action; no centrally elicited effect on the firing rate of presym pathetic sympatoexcitatory neurons in the rostral ventrolateral medulla oblongata and of splanchnic sympathetic nerve fibers was evident (Varga et al., 1996). The three studies noted above were carried out on anesthetized animals. Central sympatoexcitation was observed only in our experiments in conscious animals (Niederhofer and Szabo,
1999; and the present study). It is possible that central sympathoexcitation occurs only in the conscious but not in the anesthetized state. In agreement with this latter assumption, when cannabinoids were studied under comparable conditions in anesthetized and conscious animals, they lowered blood pressure under anesthesia but caused no change in awake animals (rats (Lake et al., 1997), dogs (Jandhyala and Hamed, 1978).

The second effect after central application of the cannabinoid agonists was a marked bradycardia. The effect was attributable to an increase in cardiac vagal activity for two reasons. First, the bradycardia produced by i.c.-administered WIN55212-2 was prevented by i.v.-administered atropine (Niederhoffer and Szabo, 1999). Similarly, the bradycardia produced by i.v.-injected WIN55212-2 was prevented by i.v.-administered methylatropine (B. Szabo, U. Nordheim, and N. Niederhoffer, unpublished observation). Second, the heart rate of conscious rabbits can only be lowered minimally by reducing cardiac sympathetic tone because the resting cardiac sympathetic tone is very low in these animals (McRitchie and Chalmers, 1981). The highest dose of WIN55212-2 and CP55940 (10 μg kg⁻¹) increased blood pressure; theoretically, operation of the baroreceptor reflex could contribute to the reduction in heart rate after this dose. Such a contribution of the baroreceptor reflex is, however, unlikely: the bradycardia after the highest dose of the cannabinoids was not greater than the bradycardia elicited by the preceding dose (1 μg kg⁻¹), which did not increase blood pressure.

Heart rate effects of centrally applied cannabinoids have been seldom studied. Based on their head cross-circulation experiments in dogs, Cavero et al. (1973b) concluded that the central effect of Δ⁹-tetrahydrocannabinol on heart rate is depressive and that both the sympathetic and the parasympathetic nervous system are involved in the response. In their experiments in cats, Vollmer et al. (1974) observed bradycardia and a decrease in cardiac sympathetic nerve activity after systemic injection and bradycardia after lateral cerebral ventricular administration of Δ⁹-tetrahydrocannabinol; the effects were attributed to a centrally elicited reduction of cardiac sympathetic tone. Our studies (Niederhoffer and Szabo, 1999; and the present study) are the first in which the heart rate effects of centrally administered cannabinoids were studied in conscious animals.

It is interesting that cannabinoids influence cardiovascular regulation at many sites (Fig. 5). As shown by our results, medullary centers regulating sympathetic and vagal nerve activity can be directly influenced. These centers are relay stations for the cardiovascular effects elicited by primary actions of cannabinoids in higher brain regions, e.g., in the mesolimbic system and hypothalamus. Cannabinoids have also marked effects on peripheral autonomic neurons. They presynaptically inhibit the release of noradrenaline from many postganglionic sympathetic neurons (Pertwee et al., 1996; Malinowska et al., 1997; Niederhoffer and Szabo, 1999), also in the heart (Ishac et al., 1996). Finally, cannabinoids inhibit vagal neurotransmission in the heart (B. Szabo, U. Nordheim, and N. Niederhoffer, unpublished observation).

How do these primary effects contribute to the overall cardiovascular response to systemic administration of cannabinoids? After systemic administration of cannabinoids in conscious humans and animals, the peripheral presynaptic inhibition of noradrenaline release seems to counteract the simultaneously occurring central sympathoexcitation; there-
fore, only moderate or no change in blood pressure is observed (see under Introduction; also see Niederhoffer and Szabo, 1999). It is remarkable that the central stimulatory and the peripheral inhibitory effects of cannabinoids on cardiac vagal tone can also counteract each other. The heart rate change after systemic cannabinoid application is determined by four primary actions: central and peripheral effects on the sympathetic and parasympathetic innervation of the heart. The relative contributions of the primary effects are different in the species, and this explains the different heart rate responses observed in different species. In conscious rabbits, low doses of systemically administered cannabinoids cause bradycardia (Niederhoffer and Szabo, 1999); this effect is probably attributable to the centrally elicited increase in cardiac vagal tone. After high doses of cannabinoids, the heart rate tends to increase (Niederhoffer and Szabo, 1999); this change in pattern may be attributable to increasing peripheral inhibition of cardiac vagal transmission. Humans generally respond with a strong tachycardia to systemic application of $D_9$-tetrahydrocannabinol (Benowitz et al., 1979; Huestis et al., 1992); this response is probably attributable to central excitation of cardiac sympathetic fibers and peripheral inhibition of cardiac parasympathetic fibers.

The major aim of this study was to characterize the receptors involved in the central cardiovascular effects of cannabinoids. In earlier studies in which central cardiovascular effects of cannabinoids were observed, $D_9$-tetrahydrocannabinol was used as an agonist (Cavero et al., 1973a,b; Vollmer et al., 1974). Because no antagonists were tested and because $D_9$-tetrahydrocannabinol elicits several cannabinoid receptor-independent effects (Howlett, 1995b), the involvement of cannabinoid receptors in the observed effects was not certain. In our previous study (Niederhoffer and Szabo, 1999), only WIN55212-2 was used without an antagonist. Several observations support involvement of cannabinoid receptors, probably of the CB$_2$ subtype, in the sympatoexcitatory and the bradycardia elicited by centrally administered cannabinoids in this study. First, the effects were elicited by WIN55212-2, an aminoalkylindole with high affinity for CB$_1$ and CB$_2$ receptors but without affinity for many neurotransmitter receptors and ion channels (Kuster et al., 1993; Pertwee, 1997). Second, WIN55212-3, an enantiomer of WIN55212-2 with very low affinity for cannabinoid binding sites (Kuster et al., 1993, Pertwee, 1997), was without effect. Third, the effects of WIN55212-2 were shared by CP55940, a bicyclic compound resembling $\Delta^9$-tetrahydrocannabinol. WIN55212-2 and CP55940 belong to different chemical classes, and the only common property of CP55940 and WIN55212-2 is their affinity for CB$_1$ and CB$_2$ cannabinoid receptors (Kuster et al., 1993; Felder et al., 1995; Showalter et al., 1996; Pertwee, 1997). Therefore, the fact that the two drugs elicited essentially the same effects supports involvement of cannabinoid receptors.

Which of the two cannabinoid receptors was involved in these effects? A role for CB$_1$ cannabinoid receptors is more likely because the CB$_1$ cannabinoid receptor antagonist SR141716A attenuated the effects of WIN55212-2. The effects of WIN55212-2 were only partially antagonized, probably because the dose of the antagonist was too low (0.5 mg kg$^{-1}$). This dose was chosen because it antagonized the effects of systemically administered WIN55212-2 in our previous study (Niederhoffer and Szabo, 1999). It is possible, however, that higher antagonist doses are needed to compete with the high local concentration of the agonist that is reached in the medulla after i.c. administration of the agonist. The sympatoexcitatory effect of i.c.-administered WIN55212-2 (0.1, 1, and 10 $\mu$g kg$^{-1}$) was also attenuated by i.c.-administered SR141716A ($10 \mu$g kg$^{-1}$) (N. Niederhoffer and B. Szabo, unpublished observation). Involvement of CB$_1$ receptors is also compatible with the distribution of cannabinoid receptors in the nervous system; the vast majority of neuronal cannabinoid receptors are CB$_1$ (compare Matsuda et al., 1993 with Munro et al., 1993 and Galiegue et al., 1995), and CB$_2$ receptors are only occasionally observed in central nervous neurons (Skaper et al., 1996). Importantly, CB$_1$ receptors are localized in the nucleus of the solitary tract and in the dorsal motor nucleus of the vagus (Mailleux and Vanderhaeghen, 1992; Matsuda et al., 1993; Tsou et al., 1998) where
their activation changes the firing pattern of neurons (Himmi et al., 1998). These nuclei were likely primary targets when the i.c.-applied cannabinoids elicited sympathoactivation and bradycardia.

In conclusion, centrally applied cannabinoids caused sympathoactivation and bradycardia in conscious rabbits. This is the first demonstration of a central sympathoexcitation by cannabinoids by direct measurement of sympathetic nerve activity. The centrally elicited cardiovascular effects were probably mediated by CB1 receptors.

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References


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