Implication of the Endocannabinoid System in the Locomotor Hyperactivity Associated with Congenital Hypothyroidism

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Alterations in motor functions are well-characterized features observed in humans and experimental animals subjected to thyroid hormone dysfunctions during development. Here we show that congenitally hypothyroid rats display hyperactivity in the adult life. This phenotype was associated with a decreased content of cannabinoid receptor type 1 (CB₁) mRNA in the striatum and a reduction in the number of binding sites in both striatum and projection areas. These findings suggest that hyperactivity may be the consequence of a thyroid hormone deficiency-induced removal of the endocannabinoid tone, normally acting as a brake for hyperactivity at the basal ganglia. In agreement with the decrease in CB₁ receptor gene expression, a lower cannabinoid response, measured by biochemical, genetic and behavioral parameters, was observed in the hypothyroid animals. Finally, both CB₁ receptor gene expression and the biochemical and behavioral dysfunctions found in the hypothyroid animals were improved after a thyroid hormone replacement treatment. Thus, the present study suggests that impairment in the endocannabinoid system can underlay the hyperactive phenotype associated with hypothyroidism. (Endocrinology 149: 2657–2666, 2008)

Thyroid hormones (T₁ and T₂) play an important role in the development and metabolism of many mammalian tissues. Most of the actions of these hormones are mediated by the binding of T₁ to specific nuclear receptors that are ligand-dependent transcription factors, which bind, in the target genes, to specific DNA sequences called thyroid hormone response elements, and regulate transcription initiation (1). Hence, the primary action of thyroid hormone is to control the expression of a limited number of genes in target cells, which ultimately will cause the physiological effects attributed to this hormone. Thyroid hormone receptors (TRs) are members of a large family of nuclear proteins that includes the receptors for steroids, retinoids, vitamin D₃, peroxisomal proliferators, and receptors with no recognized ligand known as orphan receptors (2).

The brain is an important target for thyroid hormone action, particularly during late fetal and early postnatal periods, as shown by numerous clinical and experimental data (3). In the rat brain, the expression of thyroid hormone receptors increases rapidly after birth, reaching the highest value by day 6 of postnatal life (4). Consistent with these data, thyroid hormone absence during the perinatal period leads to a profound brain damage unless replacement therapy with thyroid hormone is started very soon after birth. The consequences of the lack of thyroid hormone include, among others, a reduction in dendritic arborization, poor connectivity among neurons, impaired myelin deposition, and altered cell migration and synaptogenesis (3, 5).

The endocannabinoid system is a neuromodulatory system, which plays an important role in cognitive, affective, and motor functions in the brain (6). The basic components of this system are the cannabinoid receptor type 1 (CB₁) and its endogenous ligands, anandamide and 2-arachidonoylglycerol, which act as retrograde signaling molecules to regulate synaptic plasticity (reviewed in Ref. 7). The CB₁ receptor is a highly abundant G protein-coupled receptor, which regulates, through multiple subtypes of Gi/o proteins, the activity of adenyl cyclase, voltage-activated calcium channels, potassium channels, and mitogen-activated kinases (8). In addition to CB₁ receptors, another closely related cannabinoid receptor, the cannabinoid receptor type 2 (9), has been cloned. The cannabinoid receptor type 2 receptor is mainly expressed in immune cells and consequently mediates the immunomodulating activities of the cannabinoids. The existence of additional, not-yet-characterized cannabinoid receptors in the brain has been postulated to fully understand the activity of these substances (10). In addition to these basic constituents of the endocannabinoid system, other important components include enzymes and transporters implicated in the metabolism of anandamide and 2-arachidonoylglycerol (6).

The motor system is a target of cannabinoids as shown by...
the profound impact that cannabinoid agonists have on motor behavior and the high level of expression of CB₁ receptor in the basal ganglia and cerebellum (11). In the basal ganglia, the CB₁ receptor gene is expressed in the medium spiny neurons of the striatum and the protein accumulates in the presynaptic terminals of these neurons in the output nuclei, globus pallidus, and reticular part of the substantia nigra (12, 13). In the cerebellum, both the mRNA and protein are abundant (12, 13). It has been shown that the dopaminergic-mediated hyperactivity is modulated by the endogenous cannabinoid system (14–16). Removal of endogenous cannabinoid tone by selective blockade of CB₁ receptor potentiates dopaminergic-mediated hyperactivity. In addition, potentiation of endocannabinoid transmission with the anandamide uptake blocker AM404 reduces hyperlocomotion mediated by dopaminergic D2 receptors (14).

Alterations in motor activities are also well-characterized features of thyroid hormone dysfunctions during development, in both humans and experimental animals (17). We focused our attention in one of these features, motor hyperactivity. In humans, between 50 and 70% of the patients with resistance to thyroid hormone (RTH), a syndrome caused by the dominant inheritance of a mutated form of the TRB isoform (18), fulfill during childhood the diagnosis criteria for attention deficit with hyperactivity disorder (ADHD) (19, 20). In contrast, in the general population, only 2–5% of school-age children meet these criteria. In experimental models, transient perinatal hypothyroidism (from the end of pregnancy to weaning) causes attention-deficit and hyperactive neurobiological symptoms in adult animals (21–24). In congenital hypothyroidism (hypothyroidism induced in the perinatal life and maintained chronically), conflicting evidences regarding motor hyperactivity have been published (25, 26). In the case of perinatal hyperthyroidism, both transient and chronic models have been associated with hyperactivity in the adult life (26, 27). However, very little is known relative to the possible genes regulated by thyroid hormone, which could be implicated in the appearance of the hyperactive phenotype, although it has been suggested that alterations in the dopaminergic and noradrenergic systems can underlay the effects of thyroid hormone (25, 28, 29).

All these data have prompted us to hypothesize that the hyperactivity associated with hypothyroidism during development may be derived from alterations of the endocannabinoid system, which exerts a negative feedback that limits hyperactivity in the adult life (26, 27). This protocol ensures that the animals are hypothyroid during conception and throughout the whole experimental period including weaning. This protocol ensures that the animals are hypothyroid during conception and throughout the whole experimental period including weaning. This protocol ensures that the animals are hypothyroid during conception and throughout the whole experimental period including weaning.

Behavioral tests

The motor activity of the animals in an open-field device (100 × 100 cm) was recorded with a digital video tracking system (SMART, Panlab, Barcelona, Spain), and the time of immobility and horizontal activity were analyzed at intervals of 5 min. Twenty-four hours before any drug treatment, including normalization of thyroid hormone levels, all the animals remained 10 min in the open field to facilitate context habituation.

Real-time PCR and Northern analysis

Total RNA was purified according to the method of Chomczynski and Sacchi (32), and samples (2 μg) from the indicated rat brains areas were used for the synthesis of cDNA with the RETRoscript kit (Ambion, Austin, Tx). Real-time PCR was performed in an ABI Prism equipment using the SYBR Green PCR master mix (Applied Biosystems, Warrington, UK) and 300 nM concentrations of specific primers. The primers used for the determination of the concentration of the different transcripts were as follows: for CB₁ receptor, two different sets of primers were used (set 1, AAG GAC CTG ATG AGT CAT CCT TTC and CAG TCT GAG TCC CCC ATG CT and set 2, GGA CTA AAG ATG CTGGGAGAT and TGT AGG ATG AGG CTG GCA ATT), which synthesized fragments of 88 and 90 bp, respectively (13). Equal results were obtained with both sets of primers, suggesting that they recognize the same mRNA. For the c-fos mRNA we used the following primers: TTT TCT TTT CTC TCT AGT CTC ATG ATG TCA GC and TCC AGC ACC AGG TTA ATT CCA, which synthesized a 76-bp fragment (33). For the normalization of cDNA loading in the PCR, we ran for all the samples parallel reactions amplifying the 18S rRNA or the cyclophilin A mRNA, a gene whose expression does not change with the thyroidal state of the animal (31, 34).
Primers were CCA GTA AGT GCG GGT CAT AAG C and CCT CAC TAA ACC ATC CAA TCG G (18S rRNA) and GCC AAG TCC ATC TAC GGA GAG A and GCC AGG ACC TGT ATG CTT CAG (cyclophilin A) that synthesize a fragment of 92 and 65 bp, respectively (35, 36). In all runs, melting curves were performed to make sure that only the corresponding DNA fragment was amplified. Each RNA sample was reverse transcribed at least one time with oligo-dT and one time with pd(N)6 random hexamer and each specific sequence measured at least twice in triplicate. In adult control striatum, random primer cDNA (dilution 1:10) gave cycle threshold values of around 20, 19, and 23 for CB1 receptor, cyclophilin A, and c-fos transcripts, respectively. In the case of 18S rRNA, a dilution of 1:1000 gave cycle threshold values between 20 and 21. Northern analyses were performed as previously described (31) using a labeled rat CB1 receptor probe expanding from nt 89 to 3876 (13).

[^3H]SR141716A-binding assay

Membranes from different parts of the brain were prepared as previously described (37), resuspended in buffer B [HEPES 20 mm (pH 7.4) and MgCl2 1 mm] and stored at −80 C until use. Radioligand binding was initiated by the addition of 25 μg of protein to tubes containing 0.5 ml of buffer C (buffer B plus fatty acid free BSA 0.5%) and [^3H]SR141716A (2.5 nm) and incubated at 30 C during 90 min. The reaction was stopped with ice-chilled buffer C and rapidly filtered through GF/C filters (Whatman, Brentford, Middlesex, UK) (37). Nonspecific binding was assessed in the presence of 5 × 10−7 m cold SR141716A.

[^35S]GTPγS-membrane binding assay

Frozen membranes were thawed and 7 μg of proteins were incubated at 30 C for 20 min in buffer D [50 mm Tris-HCl, 10 mm MgCl2, 1 mm EDTA, 100 mm NaCl, 60 μm GDP, 0.2 mg/ml BSA and 50 μm phenylmethylsulfonyl fluoride (pH 7.4)]. CB1 receptor agonist was added together with [^35S]GTPγS (0.05 nm) and further incubated at 30 C during 1 h. Reaction was stopped with ice-cold buffer E [50 mm Tris-HCl, 10 mm MgCl2, 1 mm EDTA, 100 mm NaCl, 0.5% BSA (pH 7.4)] and rapidly filtered through Whatman GF/C filters. Nonspecific binding was determined in the absence of CB1 receptor agonist and the presence of 10 μm unlabeled GTPγS.

Western blot analysis

Tissues were homogenized in radioimmunoprecipitation assay buffer, and equal quantities of total protein were separated by 10% SDS-PAGE and transferred to nitrocellulose membranes, and Western analysis was performed with primary anti CB1 receptor (Alexis Biochemicals, Lausen, Switzerland) and anticyclophilin A polyclonal antibodies (Calbiochem, San Diego, CA).

Statistical analysis

Data were analyzed by ANOVA, followed by Newman-Keul’s test as post hoc or Student t test. Statistical significance was considered when P < 0.05.

Results

Motor activity

We first determined motor activity in open field in control and hypothyroid N70 rats. As shown in Fig. 1A, the locomotor score in control rats, as expected, decreases with time. In contrast, in the hypothyroid group, barely any decrease in locomotor activity with time was observed, indicating a lack of habituation and a hyperactivity-like pattern. Cumulative scores showed a 2-fold increase in the number of crossings in the hypothyroid group, compared with controls. The dopaminergic D2 agonist, quinpirole, further increased horizontal locomotion in both groups of animals. In the hypothyroid group, the number of crossings increases 5-fold between 5 and 120 min, in comparison with controls, in which only a 2-fold increase was observed (Fig. 1B). These results suggest that the activity of the endocannabinoid system could be decreased in the hypothyroid animals because it is well established that this system reduces dopaminergic-induced hyperactivity (14, 15).

Effect of hypothyroidism on the expression of CB1 receptor gene

We first determined whether hypothyroidism has any effect on the expression of CB1 receptor gene in the brain of developing animals. For that purpose, the content of CB1 receptor transcripts and [^3H]SR141716A binding were determined in different areas of the brain of control and hypothyroid 15-d-old rats (N15). At this age the effects of thyroid hormone deficiency on gene expression in the brain are most evident and they are dependent of the specific brain area analyzed (38). As shown in Fig. 2A, in
control animals the highest amount of CB₁ receptor transcripts were found in the striatum and cerebellum, followed by the cerebral cortex and hippocampus. The lowest concentration was observed in the thalamus, midbrain, and brain stem. Relative to the effect of hypothyroidism, a significant decrease on CB₁ receptor mRNA levels (49% of the control values) in the striatum and a slight increase in the hippocampus of hypothyroid animals were observed.

Next, we determined the specific binding of [³H]SR141716A in membranes prepared from the same brain areas of control and hypothyroid N15 rats. As shown in Fig. 2B, differences between control and hypothyroid animals were observed in the cerebellum and midbrain but not the other areas analyzed. The lack of differences in binding observed in the hippocampus is in contrast with the moderate increase detected in the amount of CB₁ receptor transcripts. In the cerebellum and midbrain of hypothyroid rats, [³H]SR141716A binding was only 80 and 74% of the control values. This effect of hypothyroidism is apparently in contrast with its lack of effect on the content of CB₁ receptor transcripts in the same areas. However, in the midbrain, the decrease in [³H]SR141716A binding in hypothyroid animals can be explained by the decrease in the number of CB₁ receptor transcripts observed in the striatum of the same animals. On the other hand, the described discrepancies between binding and the levels of transcripts observed in the cerebellum and hippocampus of hypothyroid neonates suggest a complex action of thyroid hormone on the expression of this gene.

In view of the previous results showing a decrease in CB₁ receptor mRNA in the striatum and a decrease in [³H]SR141716A binding in the midbrain and cerebellum of hypothyroid 15-d-old animals, we next analyzed the developmental profile of CB₁ receptor gene expression in these areas. In the striatum of control animals, the amount of CB₁ receptor transcripts increased after birth (8-fold from N5 to N15) (Fig. 3A). This increase was markedly reduced in hypothyroid animals, and therefore, significant differences were observed between control and hypothyroid rats from N15 to adult life (Fig. 3A). Regarding [³H]SR141716A binding in the striatum of control animals, a 2.6-fold increase was observed between N15 and N70 in contrast with the earlier increase detected in transcripts levels (Fig. 3A). These results suggest a higher efficiency of translation or a longer half-life of the receptors in the adult animals, compared with N15. In agreement with the observed decrease in the level of transcripts, a clear reduction in [³H]SR141716A binding was observed in striatal (Fig. 3A) and midbrain membranes (Fig. 3B) isolated from both N30 and N70 hypothyroid animals. In contrast, the lack of effect of thyroid hormone on transcript number observed in N15 midbrain was also observed in N70 (Fig. 3B). In the cerebellum, no effect of thyroid hormone on CB₁ receptor mRNA content was observed (Fig. 3C). In contrast, the binding of [³H]SR141716A to cerebellar membranes was decreased in N30, as previously observed for N15, although no differences were observed at N70, indicating that the effect of hypothyroidism was transient and occurred at a posttranscriptional level (Fig. 3C).

We next tested the response of hypothyroid animals to the acute injection of T₃ (20 μg per 100 g BW). As can be observed in Fig. 4A, the administration of T₃ rapidly increases the content of CB₁ receptor mRNA in the striatum of N15 and N70 hypothyroid rats. In the neonates, 12 h after the administration of T₃, the content of transcripts is similar to the one observed in the control animals, and after 72 h these values were twice that of the control animals. Similar results were obtained with N70 animals, indicating a rapid response of this gene to thyroid hormone administration. This response to T₃ administration correlates with the changes observed in binding in the striatum and midbrain (Fig. 4B) of N30 hypothyroid rats after the administration of the hormone.

To further substantiate these results, we next analyzed the mRNA and protein levels of CB₁ receptor in the striatum by Northern and Western blot analysis, respectively, in N70 animals. As shown in Fig. 5, a clear decrease in the amount of mRNA was observed in the striatum of hypothyroid rats. In contrast, in the midbrain the levels of CB₁ receptor mRNA...
were lower than in the striatum, and no differences between control and hypothyroid animals were found (Fig. 5A). Also, a lower amount of CB1 receptor protein was detected in hypothyroid striatum (Fig. 5C). All these results are in agreement with the RT-PCR and ligand binding results. No changes in ligand affinity were detected when control and hypothyroid membranes were compared (dissociation constant $0.9 + 0.2$ and $0.91 + 0.15$ nm in control and hypothyroid animals, respectively, data not shown).

Response to cannabinoid agonists

The results presented so far suggest that the striatum of hypothyroid animals could be less sensitive to the action of cannabinoids than control animals. We tested this hypothesis by determining the induction by WIN55212–2 of GTP binding to G proteins in striatal membranes isolated from N70 control and hypothyroid rats. We also analyzed the response to HU210 of the immediate response gene c-fos in both groups of animals. As shown in Fig. 6A, a lower GTP binding response to WIN55212–2 (3 × 10$^{-5}$ and 10$^{-5}$ m) was observed in hypothyroid membranes (69% of the control values). This decrease in GTP binding was observed with all the concentration tested (Fig. 6B), and a similar EC$_{50}$ ($0.9 + 0.12$ 10$^{-7}$ m

Fig. 3. Effect of hypothyroidism on the developmental profile of CB1 receptor gene expression in the striatum, midbrain, and cerebellum. Total RNA and membranes were isolated from striatum (A), midbrain (B), and cerebellum (C) of control (C) and hypothyroid (Tx) rats at the indicated ages and the amount of CB1 receptor transcripts and [3H]SR141716A binding determined. The relative abundance of CB1 transcripts was normalized to the 18S rRNA signal and is expressed relative to the value in N15 controls. Values are the average of triplicate determinations in at least five different samples, and the bars represent the SEs. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ vs. the corresponding control.

Fig. 4. T$_3$ induces the expression of the CB1 receptor gene. Hypothyroid rats (N15, N30, and N70) were injected with T$_3$ (20 g per 100 g BW) and killed at the indicated times. Total RNA from the striatum (N15 and N70; A) and membranes from the striatum and midbrain (N30; B) were isolated and CB1 receptor mRNA content and [3H]SR141716A binding determined. The relative abundance of CB1 transcripts was normalized to the cyclophilin A signal and are expressed relative to the values in the age-matched euthyroid controls. Values are the average of triplicate determinations in at least five different samples, and the bars represent the SEs. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ vs. the hypothyroid values. Gray bands represent the mean values ± SE of control (euthyroid) animals.
and 0.92 ± 0.14 \times 10^{-7} \text{ m}) was obtained for both control and hypothyroid membranes. These results are clearly in agreement with the lower number of CB1 receptors observed in the hypothyroid animals.

As commented above, we also analyzed the induction of the early gene c-fos by the cannabinoid receptor agonist HU210. The time course of c-fos gene in response to HU210 in the striatum and cerebellum of N70 control and hypothyroid animals is shown in Fig. 7. In the striatum of control animals (Fig. 7A), a rapid transient increase (3-fold) was observed 30 min after administration of the drug, which was completely absent in hypothyroid rats. On the contrary, in the cerebellum, in which no differences in CB1 receptor content were observed between N70 control and hypothyroid animals, the same response was observed in both groups after the injection of the cannabinoid.

Based on the biochemical results described above, it could be anticipated that the hypothyroid animals are less responsive to cannabinoid treatment. To test this hypothesis, we studied the inhibition of locomotor activity in response to HU210 in control and hypothyroid animals. As shown in Fig. 8, HU210 clearly decreased locomotor activity in the control group but not the hypothyroid group.

**Effect of thyroid hormone treatment**

As shown before in the kinetic studies, T3 injection increased CB1 receptor gene expression in the hypothyroid animals in a relatively short time, suggesting that thyroid hormone could also normalize the biochemical and behavioral parameters analyzed in this study. To verify this premise, N70 hypothyroid rats were injected with physiological doses of thyroid hormones and, after 5 d of treatment, biochemical and behavioral parameters were analyzed. This treatment, as expected, normalized the CB1 receptor mRNA in the striatum of hypothyroid animals (Fig. 9A). In accordance with the normalization of CB1 receptor mRNA content, the response of the c-fos gene to cannabinoid administration was also normalized in the striatum of hypothyroid animals treated with thyroid hormones, as shown by the transient 3-fold increase observed in c-fos transcript content (Fig. 9B). Finally, horizontal locomotor activity was clearly decreased by this treatment (Fig. 9C), and the behavioral response to cannabinoid agonist was restored in treated animals as shown by the appearance of typical motor inactivity in response to HU210 (Fig. 9D).
but lower T3 binding and transactivation capabilities and (40). The mutated protein has normal DNA binding activity.

The relative abundance of c-fos indicated times, and the amount of c-fos mRNA measured by RT-PCR. The relative abundance of c-fos transcripts was normalized to the cyclophillin A signal and expressed relative to the values at time 0. Values are the average of at least four different samples, and the bars represent the SEs. *, P < 0.05; **, P < 0.01 vs. the value at time 0.

**Discussion**

In this work we analyzed the role of the endocannabinoid system in the hyperactive phenotype observed in congenitally hypothyroid animals. Our results clearly show that the postnatal increase in CB1 receptor gene expression in the basal ganglia circuitry of control rats is thyroid hormone dependent. Thus, lower levels of CB1 receptors and a lower biochemical and behavioral response to cannabinoimetic drugs were observed in adult congenitally hypothyroid animals. These changes correlate with higher spontaneous and dopaminergic-induced locomotor activity. Because it is generally accepted that the endocannabinoid system in the basal ganglia circuitry acts as a brake in motor activity initiation (11, 15), these results suggest that the CB1 receptor gene could be an important mediator in this phenotypic manifestation of hypothyroidism, as suggested in a former study in juvenile hypothyroid mice (25) have shown increased locomotor activity in iodine-deficient congenitally hypothyroid rats. In contrast, other authors did not find any increase in motor activity (26). In the hyt/hyt mouse model of hypothyroidism, no changes in motor activity have been reported (49). The causes underlying this apparent contradiction are unclear. Although the hyt/hyt model is not entirely comparable with the one we used here, the experimental model used by Sala-Roca et al. (26) is essentially the same. One possible explanation is that the degree of hypothyroidism in the animals used in the study of Sala-Roca et al. could be very low or almost negligible during the critical developmental period because, as they point out, their animals grew normally during the first 5 wk of postnatal life. In this regard it is known that hyperactivity is a phenotypic manifestation of perinatal hypothyroidism, but it is not observed when adult rats are made hypothyroid (data not shown). Interestingly, and in agreement with the data obtained from the study of human RTH, when a mutated human TRβ (TRβPV) is expressed in mice by transgenic or knockin techniques, male animals become clearly hyperactive (50, 51).

Additionally, our data show that both hyperactivity and the abnormal response of the endocannabinoid system found in hypothyroid animals are clearly improved by physiolog-
ical doses of thyroid hormones, suggesting that the brain response to these hormones, in this particular system, is maintained in adult congenitally hypothyroid rats. The reasons that in the transient model of perinatal hypothyroidism (21–24), the hyperactive phenotype remains despite thyroid hormone normalization are unclear. However, there are many reports suggesting that perinatal manipulation of the endocannabinoid system with drugs leads to permanent changes in its functionality, resulting, among others, in hyperactivity (52), altered emotional responses (53), and memory deficits (54).

Our results are in agreement with those reported by other authors showing an inverse relationship between the activity of the endocannabinoid system and locomotor activity. The administration of cannabinoid agonists and inhibitors of anandamide and 2-arachidonoylglycerol uptake reduce hyperactivity in spontaneously hypertensive rats (14, 57) and hyperactivity induced by psychostimulants and D2 agonists (58). On the other hand, CB1 receptor antagonists favor dopamine receptor-mediated induction of motor activity (15) and stereotyped behaviors (59). Impulsive spontaneously
hypertensive rats have lower levels of CB2 receptors in the prefrontal cortex (57). Also, in reserpine-treated rats, an animal model of Parkinson’s disease, an increase in 2-AG has been described in the globus pallidus, which has been related to the suppression of locomotion in these animals, and CB1 receptor antagonists are required for a better normalization of motor activity (60). These results may apparently be in contradiction with the lack of a similar phenotype in cannabinoid CB1 receptor knockouts. However, although these animals are not hyperactive, they display abnormal dopamine-mediated behavior such as acquisition of operant responding for cocaine and opiates (61). Moreover, the selective reduction of CB1 receptors exhibited by hypothyroid rats with the global lack of CB2 receptors in different species and throughout the whole developmental period cannot be fully compared.

Collectively, our results suggest, but do not unequivocally show, that a deficit in the endocannabinoid system function in the basal ganglia could cause, at least in part, the motor hyperactivity associated with the congenital hypothyroid state, and open new research expectations in ADHD.

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