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Original article

Angiotensin converting enzyme and neprilysin inhibition alter pain response in dexhamethasone-induced hypertensive rats

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ABSTRACT

Background: We hypothesized that renin-angiotensin system and neprilysin (NEP) inhibition can modulate the nociceptive parameters on hypertensive rats. The aim of this study is to assess the preventive and therapeutic effects of ramipril and sacubitril on the pain hypersensitivities, and their interaction mechanisms with high blood pressure.
Methods: Antinociceptive effects of ramipril and sacubitril were compared with those of diclofenac. Threshold of pain assesments were recorded before drugs administration. After a 18 days treatment, normotensive and dexamethasone-induced hypertensive rats were evaluated on thermal hyperalgesia and mechanical allodynia tests. Blood pressure of rats were verified by mean arterial pressure measurement.
Results: Hypertensive rats showed significantly high pain threshold on thermal plantar test compared to that of normotensives. Among hypertensive rats, pain hypersensitivity was lowest in diclofenac group, followed by sacubitril group, while ramipril caused increased thermal and mechanical hypersensitivities.
Conclusion: We found that NEP inhibition may play a role in nociception in hypertensive rats. NEP inhibitors may be suitable choice for the management of hypertension and pain because of their therapeutic and preventive effects on nociception and arterial blood pressure.

Introduction

Hypertension is related to a diminished pain sensitivity and increased pain threshold [1–4]. Patients with essential hypertension also have increased pain tolerance to noxious thermal stimulation [4]. It is uncertain whether decreased perception of pain is due to high blood pressure or both had a common mechanistic link.

The hypoalgesia observed in chronic hypertension is associated with the changes in cholinergic, opioidergic, and noradrenergic functions [5]. Alterations of supraspinal and/or spinopetal pain modulatorys systems through sino-aortic afferents secondary to increased systemic arterial blood pressure may be a one the possible explanation of hypoalgesia observed in hypertensives [6]. Additionally hypertension related pressure alterations may induce activation of cardiopulmonary vagal afferents which alters supraspinal and/or spinopetal pain modulatory systems [7]. Unfortunately, mechanistic link between hypertension and hypoalgesia is unclear.

Angiotensin converting enzyme (ACE) and neutral endopeptidase- neprilysin (NEP) are membrane-bound zinc-containing metallopeptidases. Both enzymes share various common substrates, like bradykinin, enkephalins, chemotactic peptides and angiotensin I [8]. Angiotensin II increases systemic blood pressure. Ramipril is an ACE inhibitor which prevents the formation of angiotensin II from angiotensin I. Bradykinin is also degraded by ACE. Bradykinin stimulates the release of substance P, involved in pain transmision, through bradykinin 2 receptors [9].

NEP is found in many tissues including vascular, renal and peripheral nervous system. NEP is involved in the degradation of many neuroactive and vasoactive peptides including calcitonin-gene-related peptide, adrenomedullin, bradykinin and natriuretic peptides. Sacubitril is a prodrug that inhibits NEP through the active metabolite LBQ657. Inhibition of neprilysin increases levels of vasoactive peptides [10]. In order to prevent angioedema due to disdegradation of bradykinin, we used combination of a NEP

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inhibitor with an angiotensin receptor blocker, sacubitril/valsartan, in this study.

By inhibiting renin angiotensin sysyem (RAS) and increasing natriuretic peptide activity, NEP/ACE inhibitors may diminish vasoconstrictor and proliferative mediators, like angiotensin II and endothelin-1, and increase natriuretic peptides and bradykinin levels [8]. Still, little information is available regarding the effect of vasopeptidase inhibitors in animal models of hypertension-induced hypoalgesia.

To clarify the effects of vasopeptidase inhibitors in nociception associated with hypertension, we investigated the influence of hypertension on thermal hyperalgesia and mechanical allodynia tests in rats treated with sacubitril, NEP inhibitor, and ramipril, ACE inhibitor. This survey is the first study comparing angiotensin-neprilysin inhibition in pain thresholds in normotensive and hypertensive subjects.

Material and methods

The study was carried out at our medical pharmacology department. Animal trials were initiated after approval from the local ethics committee (Ethics Committee File No: 2017/05-01, Approval date: 06.12.2017). A total number of fourty-eight male Wistar-Albino rats (body weight 200–300 g) in eight groups were randomly selected in the study. Animals were kept at an ambient temperature of 22 °C and 60 ± 5% humidity with a 12-hr light/dark cycle and access to water and food ad libitum.

Drugs and chemicals

Diclofenac and dexamethasone were purchased from Deva, ramipril was purchased from Sanofi and sacubitril/valsartan was supplied from Novartis. Diclofenac, ramipril and sacubitril/valsartan were freshly prepared at doses of 20 mg/kg per day, 10 mg/kg/d per day and 80 mg/kg/d per day respectively, homogenously dissolved in water and administered to rats with orogastric lavage. Dexamethasone (dex, 30 μg/kg per day) and sterile saline (sodium chloride) were administered subcutanously at volume of 1 ml/kg.

Experimental design

The rats were divided randomly into eight groups: (i) saline (n = 6); (ii) diclofenac (n = 6); (iii) ramipril (n = 6); (iv) sacubitril (n = 6); (v) saline and dex (n = 6); (vi) diclofenac and dex (n = 6); (vii) ramipril and dex (n = 6); (viii) sacubitril and dex (n = 6).

In order to acclimatize to the surrounding, handling and blood pressure measurement equipment, the animals were given two weeks prior to the experiments. Pretreatment behaviors of the pain hypersensitivities (thermal hyperalgesia, mechanical allodynia) were measured. Treatment with diclofenac (20 mg/kg), ramipril (10 mg/kg), sacubitril (80 mg/kg) or saline (control) lasted for 18 days. Hypertension was induced by subcutaneous injection of dex as previously reported [11]. Briefly, on the 4. day of treatment with diclofenac, ramipril, sacubitril or saline (control), the rats were additionally injected with dex (30 μg/kg per day) for 14 days. After treatments, groups were assessed for their response to nociception on thermal hyperalgesia and mechanical allodynia tests. Arterial blood pressure were verified by MAP (mean arterial pressure) measures.

Evaluation of mechanical allodynia (Dynamic Plantar Aesthesiometer)

We used automated version of von Frey hair test, the Dynamic Plantar Aesthesiometer test (Ugo Basile, Comerio, Italy), for the evaluation of animal sensitivity to the non-noxious light touch of the paw. This test was performed according to the previously reported method [12]. Mechanical allodynia is defined as the brisk paw withdrawal in response to mechanical stimulus due to significant decrease in threshold. Rats were placed in individual plexiglass boxes on a stainless steel mesh floor. A force of 2.5 g/s was applied *via* a 0.5 mm diameter straight metal filament to the plantar surface of hindpaw until animal lifts its foot. When the animal lift its foot, paw-withdrawal threshold was digitally recorded in grams. Mechanical stimulus was automatically turned off to avoid tissue damage when 50 g cut-off force was reached.

Evaluation of thermal hyperalgesia (Thermal Plantar Test)

Thermal stimulation system (Commat, Ankara, Turkey) was used for the evaluation of thermal hyperalgesia by measuring paw withdrawal latency. This test was performed according to the method previously described [13]. To acclimatize to the testing enviroment animals were allowed at least 10 min in plexiglass chambers (10 cm x 20 cm x 24 cm) on a clear glass platform. Termal stimulus was delivered to the mid plantar region right or left hind paws through a radiant heat source mounted on a movable holder below a glass pane. When the rat feels pain and withdraws its paw, infrared generator is turned off automatically, and timer stops, determining the withdrawal latency. If the rat fails to withdraw its paw, thermal source is automatically swithed off after 25 s (cutt-off latency) to avoid injury.

Assesment of mean arterial blood pressure (MABP)

Arterial blood pressure and heart rate of all rats were measured according to previously described method at the end of the treatment [14]. Intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg) was used for anesthesia. To facilitate spontaneous breathing during the procedure, trachea was exposed and cannulated. Carotid artery was cannulated to measure invasive arterial blood pressure. Pressure measurement was recorded with MP35 Biopac System Transducer.

Data analysis

The data was defined as arithmetic mean and standard deviation. In order to apply parametric tests, Kolmogorov Smirnov test was used to determine whether the samples had normal distribution and whether the variances were homogeneous. Repeated sample test and Wilcoxon signed-rank test were used for the analysis of dependent repeated samples which ever is appropriate. For multiple groups, analysis of variance test with *post-hoc* Tukey's test for significance difference was used for normally distributed data. Kruskal Wallis test with Mann Whithney U test under Bonferroni correction was used for the analysis of none normally distributed data. The p values less than 0.05 were considered significant. The data was evaluated at the 95% confidence interval.

Results

In this study, male Wistar-Albino rats were used only. In the sensory tests, thermal hyperalgesia and mechanical allodynia were eveluated by noxious heat stimulation or non-noxious mechanical stimulation.

The effect of blood pressure on mechanic and heat hypersensitivity

Sacubitril, ramipril and diclofenac showed significant decrease in arterial blood pressure measured by carotis cannulation,

compared to that of control saline group ($p < 0.05$) (Fig. 1A). Basal termal latencies and mechanical thresholds were similar between groups. In the pre-treatment normotensive rats, the mean baseline thermal latency was 11.12 ± 1.70 s (Table 1) and the mean mechanical threshold was 30.64 ± 5.29 g (Table 2). Thermal latency and mechanical threshold did not significantly change after saline injection ($p = 0.832$ and $p = 0.258$, respectively). In the pre-treatment hypertensive rats, the mean baseline thermal latency was 10.31±0.91 s (Table 1) and the mean mechanical threshold was 31.64 ± 4.71 g (Table 2). Thermal latency significantly changed ($p = 0.007$), but mechanical threshold did not change after saline injection ($p = 0.839$).

Hypertension increased the latencies significantly on thermal plantar test ($p < 0.05$) (Fig. 1C), but did not significantly change the pain thresholds on dynamic plantar test ($p > 0.05$) (Fig. 1B).

The effect of diclofenac on mechanic and heat hypersensitivity

Administration of diclofenac caused an increase in the thermal latency to noxious thermal stimulus and the mechanical threshold to non-noxious mechanical stimulus. Diclofenac significantly enhanced the latency to 14.79 ± 1.96 s and threshold to 45.29±1.99 g in intact rats ($p < 0.05$); latency to 15.03±1.41 s and threshold to 45.66±4.13 g in hypertensive rats ($p < 0.05$). The alterations in latencies and thresholds produced by diclofenac are shown in Tables 1 and 2.

The effect of ramipril on mechanic and heat hypersensitivity

Ramipril caused increase in thermal and mechanical hypersensitivities (hyperalgesia and allodynia). Ramipril significantly decreased the thermal latency to 9.42 ± 1.90 s and mechanical threshold to 30.33±5.42 g in intact rats ($p < 0.05$), and significantly decreased the thermal latency to 8.93±0.89 s and mechanical threshold to 31.63±4.74 g in hypertensive rats ($p < 0.05$). The influence of sacubitril on the paw withdrawal latencies to thermal and mechanical stimuli are demonstrated in Tables 1 and 2. The significant decrease of response in thermal and mechanical allodyne tests produced by ramipril and the analgesic responses of diclofenac are shown in Fig. 2A and B.

The effect of sacubitril on mechanic and heat hypersensitivity

Administration of sacubitril produced an increase in the thermal latency to noxious thermal stimuli and the mechanical threshold to non-noxious mechanical stimulus ($p < 0.05$). Sacubitril enhanced latency to 13.17±1.54 s ($p > 0.05$) and significantly enhanced threshold to 43.21±6.26 g in intact rats ($p < 0.05$). Sacubitril significantly enhanced the latency to 12.63±1.18 s and threshold to 42.89±4.71 g in hypertensive rats ($p < 0.05$). The influence of sacubitril on the paw withdrawal latencies to thermal and mechanical stimuli are demonstrated in Tables 1 and 2. The significant increase of response in thermal and mechanical allodyne tests produced by sacubitril and the analgesic responses of diclofenac are shown in Fig. 3A and B.

Table 1
Paw withdrawal latency on the thermal plantar test.

Variable	Pretreatment (s)	Posttreatment (s)	*p*
Intact control	11.55 ± 1.54	11.70 ± 0.51	0.832
Intact diclofenac	11.87 ± 1.69	14.79 ± 1.96	0.004
Intact ramipril	10.72 ± 1.91	9.42 ± 1.90	0.037
Intact sacubitril	10.36 ± 1.69	13.17 ± 1.54	0.053
HT control	10.76 ± 1.10	11.80 ± 1.01	0.007
HT diclofenac	10.22 ± 1.30	15.03 ± 1.41	0.009
HT ramipril	10.03 ± 0.74	8.93 ± 0.89	<0.001
HT sacubitril	10.26 ± 0.52	12.63 ± 1.18	0.014

HT: Hypertensive.

Table 2
Mechanical pain threshold on the dynamic plantar test.

Variable	Pretreatment (g)	Posttreatment (g)	*p*
Intact control	28.66 ± 7.35	31.36 ± 5.50	0.258
Intact diclofenac	29.51 ± 5.02	45.29 ± 1.99	0.002
Intact ramipril	32.93 ± 6.51	30.33 ± 5.42	0.006
Intact sacubitril	31.48 ± 2.30	43.21 ± 6.26	0.013
HT control	32.75 ± 6.20	32.20 ± 7.46	0.839
HT diclofenac	30.12 ± 3.44	45.66 ± 4.13	0.004
HT ramipril	34.18 ± 4.86	31.63 ± 4.74	0.004
HT sacubitril	29.51 ± 4.34	42.89 ± 4.71	0.001

HT: Hypertensive.

Discussion

We assessed the preventive and therapeutic effects of ramipril and sacubitril by investigating their actions on pain hypersensitivities, and their interaction mechanisms with hypertension, in this study. We used dexamethasone-induced hypertension model since adrenocorticotropic hormone (ACTH) and adrenocortical steroids cause elevated blood pressure [15]. ACTH causes hypertension in association with a rise in cardiac output, extracellular fluid volumes and exchangeable sodium. The rise in pressure is adrenally dependent. Synthetic steroids, such as dexamethasone, induce hypertension without causing increasing plasma volume and urinary sodium retention [16]. We used invazive carotid artery cannulation techniques to measure mean arterial blood pressure in this study, because it is an accurate methodology in measuring blood pressure. Sacubitril, ramipril and diclofenac showed significant decrement in arterial blood pressure, whereas the arterial blood pressure of rats treated with sacubitril was similar to those treated with ramipril.

Pain sensitivity was negatively correlated with blood pressure levels in thermal plantar test, in our study. Baroreflex system may

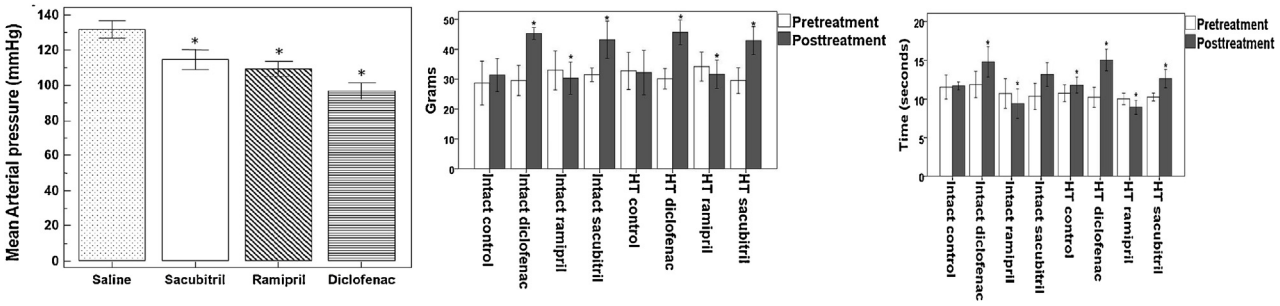

Fig. 1. A. Changes in blood pressure, B. Mechanical threshold, C. Heat hypersensitivity. Error bars represents ±SD. *$p < 0.05$, shows significant difference.

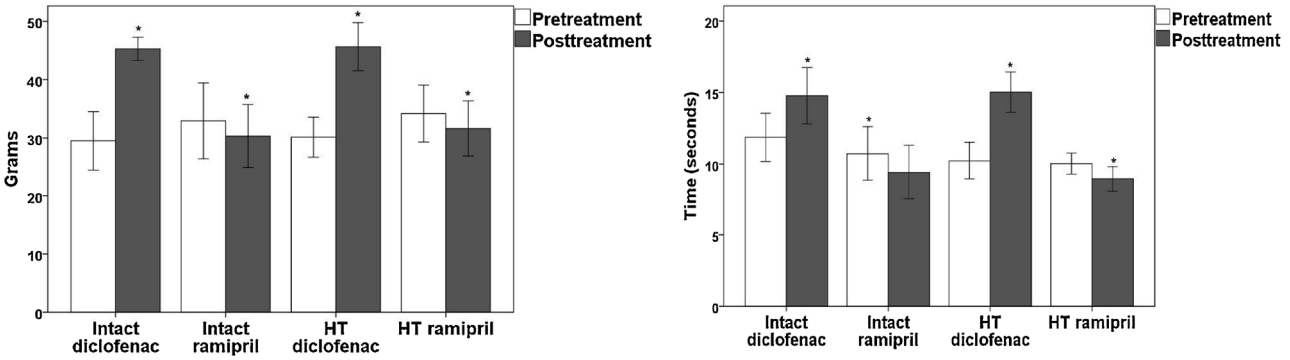

Fig. 2. Effect of ramipril and diclofenac on mechanic (Fig. 2A) and heat (Fig. 2B) hypersensitivity. Error bars represents ± SD. *$p < 0.05$, shows significant difference compared to pretreatments.

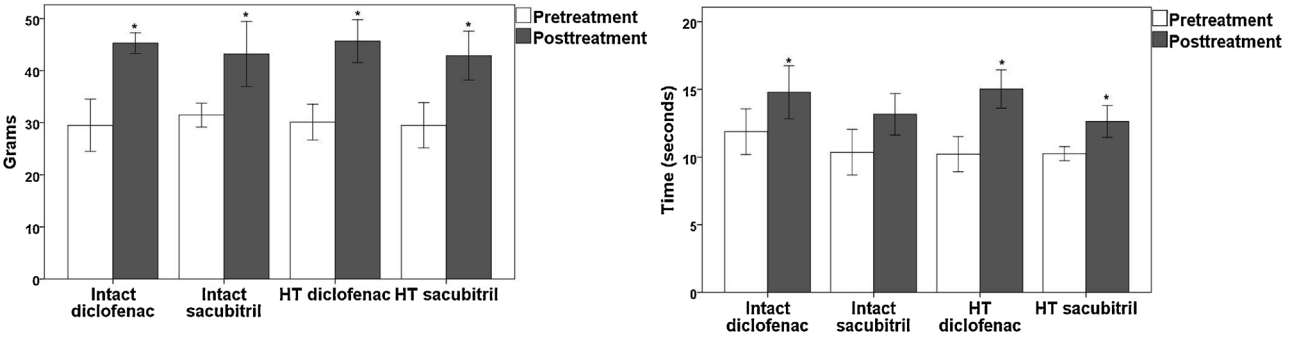

Fig. 3. Effect of sacubitril and diclofenac on mechanical threshold (Fig. 3A) and heat (Fig. 3B) hypersensitivity. Error bars represents mean ± SD. *$p < 0.05$, shows significant difference compared to control.

have a role in regulation of nociception. Baroreceptor activation induced descending inhibitory influences in cardiovascular regulation may cause decreased transmission of noxious stimuli at the spinal level. Endorphinergic, noradrenergic neurons and other mediators have been shown to be involved in hypertension-related hypalgesia [2].

Inhibition of NEP raises levels of several endogenous vasoactive peptides, including natriuretic peptides. Enhancement of natriuretic peptides (mainly brain and atrial type natriuretic peptide [BNP and ANP respectively]) are involved in common processes that have been shown to be effective in prevention of inflammation [17]. BNP and natriuretic peptide receptor A (NPRA) are upregulated after peripheral tissue inflammation. NPRA and BNP may act as an endogenous pain-relieving signal system. Thus, BNP secreted from nociceptive afferent neurons might be an endogenous analgesic molecule for inflammatory pain and might inhibit the pain response after peripheral inflammation [18].

Sensory neurons, which express adenosine triphosphate (ATP)-gated P2 × 3 receptors and/or transient receptor vanilloid-1 (TRPV1) channels, are the pain transducers of noxious stimuli. Endogenous neuropeptides upregulate their activity in acute and chronic pain. Vilotti et al. reported that, BNP was a negative regulator of trigeminal sensory neuron excitability on TRPV1 and P2 × 3 receptors [19]. Our results for the increased pain threshold under sacubitril treatment may contribute to these previous studies.

Chronic injury of peripheral nerve endings lead to the activation of sympathetic nervous system, and enhance the activation of RAS [20]. Additionally, angiotensin has an important role in neuronal injury [21]. The RAS antagonists improve syptoms of neuropathic pain [22]. ACE inhibitors increase the bradykinin levels and this may result in increase pain sensitivity through bradykinin receptors. Bradykinin, an endogenous peptide catabolised by ACE, has potent physiological effects, including increased vascular permeability, decreased blood pressure and involved in the inflammation by its effects of vasodilation, hyperthermia, edema and pain. Besides ACE, other enzymes including endothelin-converting enzyme, neprilysin, carboxypeptidase, aminopeptidase P, propyl oligopeptidase and dipeptidyl peptidase IV degrade bradykinin [23]. Bradykinin shows pronociceptive and antinociceptive activity in a dose dependent fashion. Inflammatory events, such as tissue damage and allergic reactions induce a series of proteolytic reactions and produce bradykinin formation in the tissues, which successively stimulates primary afferent neurons. Bradykinin activates nociceptors by secretion of cytokines, nitric oxide and prostaglandins, either from fibroblasts, sensory neurons, endothelium or cells of the immune system, following its interaction with mast cell mediators [24].

RAS-mediated release of angiotensin II has an important role in the evolution of pain sensitivity through angiotensin I-II receptors. The RAS is activated in neuropathic pain disorders owing to the peripheral nerve injury at the level of sympathetic outflow and dorsal root ganglion [25]. Jaggi et al reported that, angiotensin AT (1) receptor blockers improve neuropathic pain, [26]. Angiotensin II causes neuronal inflammation by induction of free radical associated lipid peroxidation formation [26]. Angiotensin II related nociceptive pain is improved by angiotensin 1–7 (AT1-7) peptide through inhibition of Mas receptors associated p38 MAPK phosphorylation. Therefore, ACE inhibitors show anti-inflammatory activity by reducing angiotensin II formation [27].

Despite the rationale of ACE inhibitors reduces angiotensin II formation, Miura et al showed that ACE inhibitors inactivated the opioid peptide [Leu5] enkephalin [28]. We found that ramipril, which also produces neuroprotection by anti-inflammatory actions and free radical scavenging, caused an increase in thermal

and mechanical sensitivities in rats. Ismael et al reported that, ramipril has favorable effects on diabetic sensory neuropathy in rats through down regulation of pro-nociceptive kinin B1 receptors [29]. In that study, tactile and cold allodynia-induced pain were studied in chronic glucose fed rats and the dosage of ramipril was 1 mg/kg/d. While in the present study the dosage of ramipril was 10 mg/kg/d and thermal and mechanical allodynia tests were performed. The peripheral nerve injury causes increased supraspinal sympathetic tone which succesively leads to excessive activation of RAS and release of pronociceptive peptides (angiotensin II). Additionally, ACE inhibitor therapy in hypertensive rats, causes increased pain sensitivity, decreased sympathetic tone through ACE inhibition and reduced endogenous opioid peptides. Salo et al reported that, ramipril therapy improved the autonomic control by reduction of sympathetic tone but did not alter endogenous opioid peptide levels [30]. We found that it significantly decreased the pain threshold in rats.

In conclusion, these data suggest that inhibition of NEP resulted in a significant improvement of nociception beyond that observed with inhibition of ACE alone. Sacubitril/valsartan has a potential ameliorating role in thermal and mechanical hyperalgesia in rats. This finding was likely partly mediated by a significant reversal of upregulation of natriuretic peptides. Therefore sacubitril/valsartan may be an appropriate choice for the management of nociception and hypertension due to its therapeutic and preventive effects on nociception. Additional mechanistic studies are needed to further elucidate the molecular pathways by which neprilysin inhibition mediates antinociceptive effects.

Conflict of interest

There is no conflict of interest and grant support.

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