Dipeptidyl peptidase IV deficiency increases susceptibility to angiotensin-converting enzyme inhibitor–induced peritracheal edema

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Background: Serum dipeptidyl peptidase IV (DPPIV) activity is decreased in some individuals with ACE inhibitor–associated angioedema. ACE and DPPIV degrade substance P, an edema-forming peptide. The contribution of impaired degradation of substance P by DPPIV to the pathogenesis of ACE inhibitor–associated angioedema is unknown.

Objectives: We sought to determine whether DPPIV deficiency results in increased edema formation during ACE inhibition. We also sought to develop an animal model using magnetic resonance imaging to quantify ACE inhibitor–induced edema.

Methods: The effect of genetic DPPIV deficiency on peritracheal edema was assessed in F344 rats after treatment with saline, captopril (2.5 mg/kg), or captopril plus the neurokinin receptor antagonist spantide (100 μg/kg) by using serial T2-weighted magnetic resonance imaging.

Results: Serum dipeptidyl peptidase activity was dramatically decreased in DPPIV-deficient rats ($P < .001$). The volume of peritracheal edema was significantly greater in captopril-treated DPPIV-deficient rats than in saline-treated DPPIV-deficient rats ($P = .001$), saline-treated rats of the normal substrain ($P < .001$), or captopril-treated rats of the normal substrain ($P = .001$). Cotreatment with spantide attenuated peritracheal edema in captopril-treated DPPIV-deficient rats ($P = .005$ vs captopril-treated DPPIV-deficient rats and $P = .57$ vs saline-treated DPPIV-deficient rats).

Conclusions: DPPIV deficiency predisposes to peritracheal edema formation when ACE is inhibited through a neurokinin receptor–dependent mechanism. Magnetic resonance imaging is useful for modeling ACE inhibitor–associated angioedema in rats.

Clinical implications: Genetic or environmental factors that decrease DPPIV activity might increase the risk of ACE inhibitor–associated angioedema. (J Allergy Clin Immunol 2007;120:403-8.)

Key words: *Angioedema, angiotensin-converting enzyme inhibitor, dipeptidyl peptidase IV, trachea, larynx, magnetic resonance imaging, pharmacogenetics, substance P, neurokinin, spantide*

Angiotensin-converting enzyme (ACE) inhibitors have been used successfully to treat patients with hypertension, congestive heart failure, and diabetic nephropathy, as well as patients at high risk for cardiovascular events.[1-4] Approximately 0.7% of patients who take ACE inhibitors experience angioedema, most often manifested by swelling of the lips or tongue.[5] The mechanism of this adverse effect is unknown. Activation of the endogenous kallikrein-kinin system contributes to hereditary forms of angioedema.[6] ACE degrades bradykinin, leading many to implicate bradykinin in the pathogenesis of ACE inhibitor–associated angioedema.

In addition to affecting vascular permeability directly, bradykinin stimulates the release of substance P,[7] a vasoactive peptide that acts through neurokinin 1 receptors to produce vasodilatation and protein and fluid extravasation in tissues in animal models.[8] ACE and neutral endopeptidase (NEP; EC 3.4.24.11) degrade substance P.[9] However, in the setting of ACE inhibition, dipeptidyl peptidase IV (DPPIV) plays the primary role in the degradation and inactivation of substance P. In fact, dual inhibition of ACE and DPPIV inhibits substance P hydrolysis by nearly 90% in rat plasma.[10] Some individuals who experience ACE inhibitor–associated angioedema have lower serum DPPIV enzyme activity than do control subjects who tolerate ACE inhibitors without angioedema,[11] suggesting the hypothesis that angioedema might result from impaired degradation of substance P by DPPIV.

The availability of Fisher F344 rats that lack active DPPIV enzyme[12] from specific colonies in Japan and Germany provides a convenient animal model in which to study DPPIV deficiency. The development of an *in vivo* animal model of ACE inhibitor–associated angioedema would enhance the ability of investigators to explore the mechanisms underlying this adverse event.

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Abbreviations used
ACE: Angiotensin-converting enzyme
DPPIV: Dipeptidyl peptidase IV
DPPIV$^-$: Fisher F344/DuCrlCrlj DPPIV–deficient rats from Japanese colonies
DPPIV$^+$: Fisher F344/DuCrl rats with normal DPPIV activity from American colonies
MAP: Mean arterial pressure
MRI: Magnetic resonance imaging
NEP: Neutral endopeptidase

Measurement of the extravasation of Evans blue dye has been used to quantify tracheal edema in rats[13]; however, this method requires the death of the animal and surgical manipulation of the trachea. Magnetic resonance imaging (MRI) has been used extensively in the characterization of edema in various body tissues, both in human subjects and in animal models, making it a logical choice for evaluation of edema in the tracheal region in a rat model of ACE inhibitor–associated angioedema. In addition, there is a case report of the use of MRI to image human angioedema.[14] This study tests the hypothesis that rats lacking DPPIV demonstrate increased tracheal edema after administration of an ACE inhibitor, as measured by means of MRI.

METHODS

Animals

Male Fisher F344/DuCrlCrlj DPPIV-deficient (DPPIV$^-$) rats were obtained from Charles River Japan (Tokyo, Japan). Male Fisher F344/DuCrl (DPPIV$^+$) rats were obtained from Charles River Laboratories (Wilmington, Mass). Rats were housed in a temperature- and humidity-controlled environment, with free access to standard rat chow and tap water. All experiments were carried out according to the guidelines in the "Guide for the care and use of laboratory animals" (http://www.nap.edu/readingroom/books/labrats/) prepared by the Institute of Laboratory Animal Resources, and the protocol was approved by the Vanderbilt University Institutional Animal Care and Use Committee.

DPPIV activity assay

Blood for determination of DPPIV activity was collected by means of terminal exsanguination in the absence of anticoagulant, centrifuged immediately, and stored at −80°C until assay. DPPIV activity was assayed by incubating sera with a colorimetric substrate, L-glycyl-L-prolyl *p*-nitroanilide (Sigma, St Louis, Mo), at 37°C, as previously described.[15]

MRI protocol

After achievement of anesthesia with pentobarbital (50 mg/kg administered intraperitoneally), femoral arterial and venous Micro-Renathane catheters (Braintree Scientific, Braintree, Mass) were inserted and tunneled to exit the skin near the neck. Animals were allowed to recover from the pentobarbital before the MRI study.

A total of 13 DPPIV$^+$ rats were then randomized to one of 2 treatment groups: vehicle plus vehicle (control) or vehicle plus the ACE inhibitor captopril (2.5 mg/kg). Twenty-one DPPIV$^-$ rats were randomized to these 2 treatments, as well as a third treatment group consisting of the neurokinin receptor antagonist spantide (100 μg/kg) plus captopril. All drugs were administered intravenously in equivalent volumes. Vehicle or spantide was administered 1 minute before administration of captopril or vehicle.

All MRI data were collected at the Vanderbilt University Institute of Imaging Science, Center for Small Animal Imaging. During MRI, rats were anesthetized with 2% isoflurane in oxygen, and temperature was monitored and maintained near 37°C. Images were acquired with a Varian 7 Tesla MRI scanner by using a T2-weighted fast-spin echo technique. A 63-mm-diameter coil was used for radiofrequency transmission and reception. At each time point, 24 contiguous 1-mm-thick slices were acquired, starting from the trachea near the carina and scanning in a cranial direction to include part of the oropharynx. Images had a field of view of 60 mm × 60 mm encoded with 256 × 256 samples, and 4 acquisitions were averaged. Respiratory gating defined the repetition time of every other breath (approximately 4 seconds), resulting in an acquisition time of approximately 10 minutes per time point. Two baseline time points were acquired before administration of the drug. After drug administration, MRI sequences were obtained every 10 minutes for at least 1 hour. Rats were killed by means of exsanguination at the end of image acquisition. Because of a malfunction of the VNMRj software controlling the Varian scanner, slices were spatially interleaved only in some studies (n = 12). The occurrence of interleaving did not vary by treatment group ($P = .70$, 1-way ANOVA).

Image analysis

Image coregistration was achieved by using a variant of the Mutual Information Algorithm, publicly available from the National Library of Medicine's Insight Toolkit (http://www.itk.org). An investigator who was unaware of treatment drew a region of interest around the trachea and a separate region of interest around a muscle region distant from the trachea on each slice using MATLAB (The MathWorks, Inc, Natick, Mass). The area of edema was defined as that area showing signal intensity at least 2 SDs greater than the signal intensity of muscle after subtracting the baseline area of high intensity. Statistical analysis was performed on the sum of these adjusted areas across all 24 slices for a given time point. This summary change score was the primary outcome variable, as measured in voxels. Each voxel contained 0.0549 mm^3 of tissue.

Blood pressure measurement

In a separate protocol blood pressure response to ACE inhibition was compared in DPPIV$^-$ and DPPIV$^+$ rats. Femoral arterial and venous catheters were placed after achievement of anesthesia with pentobarbital (42.5 mg/kg administered intraperitoneally). Arterial blood pressure was measured in the femoral artery by using a Micro-Med (Micro-Med, Louisville, Ky) blood pressure analyzer. Rats were randomized to receive vehicle plus vehicle, vehicle plus captopril (2.5 mg/kg), vehicle plus captopril plus the NEP inhibitor thiorphan (3.5 mg/kg), or vehicle plus captopril plus thiorphan plus spantide (600 μg/kg) intravenously.

Statistical methods

Data are presented as means ± SEM. Enzyme activity was compared by using the Student *t* test. Data for the area of edema for each slice were graphed to assess for outliers caused by, for example, registration error. Outliers were defined mathematically as those values more than 2 SD+2 beyond the mean for the same treatment group. By using this method, 48 (0.6%) of the 7709 data points for change in edema from baseline were identified as outliers. These outliers were replaced with values interpolated from the area of edema in the 2 anatomically adjacent slices for the same animal. The effects of

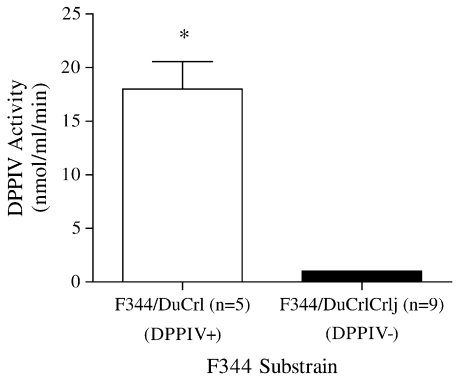

FIG 1. DPPIV activity in DPPIV$^-$ rats from Japan and DPPIV$^+$ rats from a domestic source. *$P < .001$ versus DPPIV$^-$ rats.

rat substrain and treatment were compared by using repeated-measures ANOVA, in which the within-subject variable was time and the between-subject variables were group, the presence or absence of interleaving, and coil adjustment. Repeated-measures ANOVA was followed by *post hoc* comparisons. Statistical analysis was performed with SPSS version 15.0.0 (SPSS, Inc, Chicago, Ill).

RESULTS

DPPIV activity

DPPIV enzyme activity was assayed in the sera from 9 DPPIV$^-$ rats obtained from Japan and 5 DPPIV$^+$ rats obtained from a domestic source (Fig 1). Enzyme activity was significantly lower in the DPPIV$^-$ rats than in the DPPIV$^+$ rats (1.2 ± 0.2 vs 17.8 ± 2.8 nmol/mL/min, $P < .001$).

Edema response

As shown in Fig 2, serial slices were obtained from a region of the trachea near the carina to the caudal portion of the oropharynx. Total area of the peritracheal regions of interest was similar among all treatment groups ($P = .69$, 1-way ANOVA). Fig 3 shows the evolution of edema with narrowing of the airway in a captopril-treated DPPIV$^-$ rat. By using repeated-measures ANOVA, the volume of edema differed significantly with time ($P < .001$) and among groups ($P = .001$). By means of *post hoc* comparison, the development of edema over time was significantly greater in the captopril-treated DPPIV$^-$ rats (estimated marginal mean, 94.5 voxels) than in the saline-treated DPPIV$^-$ rats (26.6 voxels, $P = 0.001$), the saline-treated DPPIV$^+$ rats (2.7 voxels, $P < .001$), the captopril-treated DPPIV$^+$ rats (25.4 voxels, $P = .001$), and the captopril plus spantide–treated DPPIV$^-$ rats (37.2 voxels, $P = .005$; Fig 4). In contrast, there was no significant difference in volume of edema between the captopril-treated DPPIV$^-$ rats cotreated with the neurokinin receptor blocker spantide I and the saline-treated DPPIV$^-$ rats ($P = .57$), the captopril-treated DPPIV$^+$ rats ($P = .53$), or the saline-treated DPPIV$^+$ rats ($P = .09$).

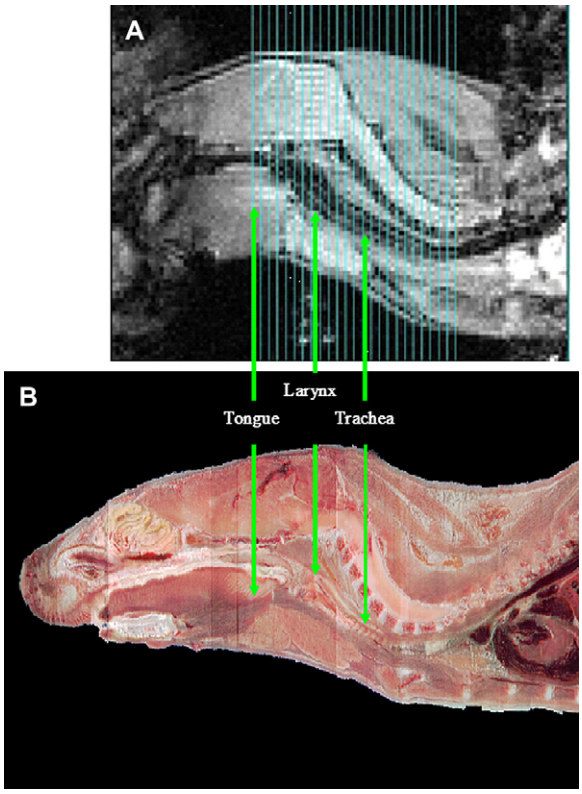

FIG 2. The anatomy scanned in the MRI studies. **A** shows a scout MRI scan in the sagittal view. *Blue lines* indicate the position of the 24 MRI slices. For comparison, **B** shows a sagittal cryosection through a rat in the same region. Cryosection image from the SD Rat Atlas Project (http://vchibp.vicp.net/vch/mice/) is used with permission.

Blood pressure response

Baseline mean arterial pressure (MAP) was similar in the DPPIV$^-$ versus the DPPIV$^+$ rats (Fig 5). Likewise, the effect of captopril on MAP was similar in the DPPIV$^-$ versus the DPPIV$^+$ rats. However, when ACE and NEP were inhibited concurrently by using captopril and thiorphan, MAP was significantly less in the DPPIV$^-$ rats compared with in the DPPIV$^+$ rats ($P = .045$). Likewise, MAP was significantly less in the captopril plus thiorphan–treated DPPIV$^-$ rats compared with in the saline-treated rats ($P = .01$). Cotreatment with spantide significantly increased MAP in the captopril plus thiorphan–treated DPPIV$^-$ rats ($P = .03$ compared with the captopril plus thiorphan–treated DPPIV$^-$ rats without spantide).

DISCUSSION

DPPIV activity is decreased in the sera of some patients with acute ACE inhibitor–associated angioedema. Nevertheless, the role of DPPIV in the pathogenesis of ACE inhibitor–associated angioedema has not been defined. The current study represents the first *in vivo* demonstration that DPPIV deficiency can contribute to ACE inhibitor–

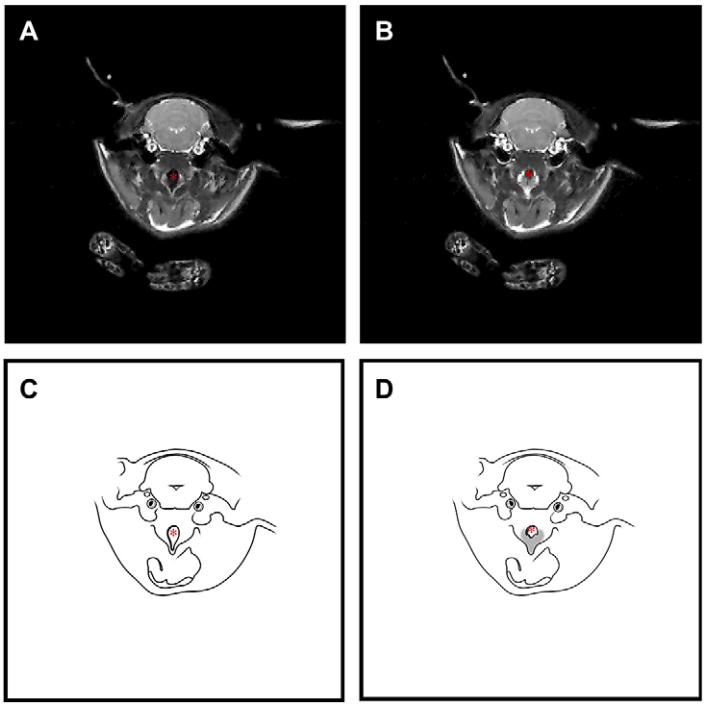

FIG 3. T2-weighted MRI image and corresponding line drawing of vocal cords at baseline (**A** and **C**) and at 50 minutes (**B** and **D**) after injection of captopril in a DPPIV$^-$ rat. Fig 3, *B* and *D*, show the development of vocal cord edema. The *red asterisks* illustrate the airway at the level of the vocal cords in these transverse slices.

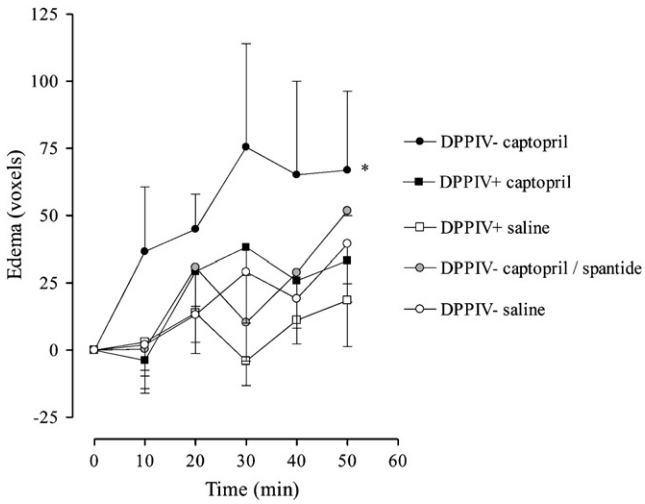

FIG 4. Effect of captopril on tracheal edema in DPPIV$^-$ and DPPIV$^+$ rats. Edema formation was significantly greater in captopril-treated DPPIV$^-$ rats than in any other treatment group (see text).

induced tracheal edema. The finding that coadministration of a neurokinin receptor antagonist counteracted peritracheal edema formation in ACE inhibitor–treated DPPIV$^-$ rats suggests that substance P plays a role in the pathogenesis of the edema. These findings are consistent with those of Emanueli et al,[13] who found that the NK1 antagonist SR140333 attenuated plasma extravasation in tracheal and other tissues of mice treated with captopril. The findings are also consistent with the observation that substance P metabolism is impaired by pharmacologic inhibition of DPPIV in rats, particularly in the setting of ACE inhibition.[16]

This study also examined the effect of genetic deficiency of DPPIV on ACE inhibitor–induced hypotension. Although DPPIV deficiency enhanced captopril-induced peritracheal edema formation, DPPIV deficiency potentiated the hypotensive effect of captopril only when NEP was inhibited concurrently. Vasodilation leading to the observed hypotension might account for some of the edema formation in the peritracheal area, although

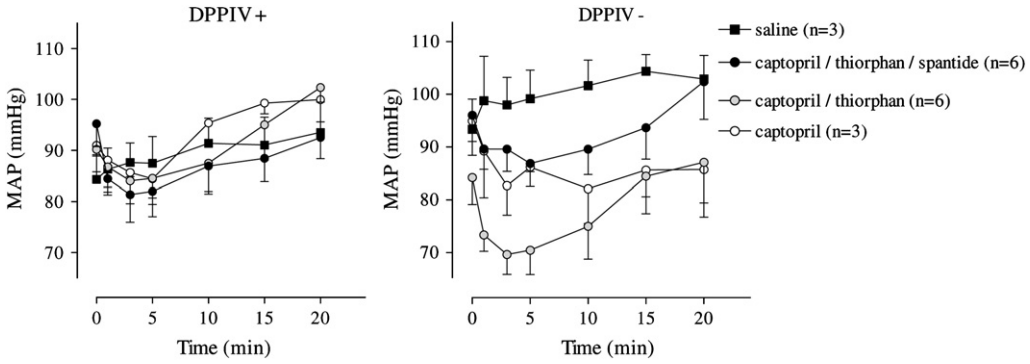

FIG 5. Effect of treatment on blood pressure in DPPIV$^+$ and DPPIV$^-$ rats. MAP was significantly less in captopril plus thiorphan–treated DPPIV$^-$ rats compared with that in saline-treated DPPIV$^-$ rats ($P = .01$) or captopril plus thiorphan–treated DPPIV$^+$ rats ($P = .045$). Spantide significantly increased MAP in captopril plus thiorphan–treated DPPIV$^-$ rats ($P = .03$).

hypotension occurred only in the setting of concurrent ACE and NEP inhibition. Peritracheal edema, on the other hand, was seen in DPPIV$^-$ animals treated solely with captopril. These data might reflect tissue differences in the contribution of NEP to the degradation of substance P.[17] The finding that spantide I increased pressure in the captopril plus thiorphan–treated DPPIV$^-$ animals suggests that substance P contributes to hypotension in the model.

In addition to elucidating the role of DPPIV deficiency and substance P in ACE inhibitor–induced edema in the trachea and larynx, this study establishes the feasibility of using MRI to visualize ACE inhibitor–induced tracheal edema in an animal model. Evidence supports the relevance of animal models of peritracheal edema to human angioedema. ACE inhibitors cause peritracheal edema in rodents when used at doses similar to those used in human subjects.[13,18] In addition, animal models of peritracheal edema have recapitulated the phenotype of human angioedema[19] in that dual inhibition of ACE and NEP causes increased edema when compared with ACE inhibition alone.[20] The development of an animal model of ACE inhibitor–induced edema provides the opportunity to further define the pathophysiology of this disorder, to understand how environmental factors (eg, smoking) modify risks, to develop strategies to identify patients at risk for angioedema, and to screen new drug entities for their potential to cause angioedema.

The results of this study have implications for the development and use of a new class of antidiabetic agents. The first DPPIV inhibitor, sitagliptin, has recently been approved for use in type 2 diabetes mellitus. In addition to degrading bradykinin (2-9) and substance P, DPPIV cleaves the incretins glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 ([7-36] amide).[21] Moreover, DPPIV activity is increased in the setting of hyperglycemia.[22] Animal studies[23-25] and clinical trials[26-29] demonstrate that DPPIV inhibition improves glucose tolerance. Interestingly, in the Omapatrilat Cardiovascular Treatment vs. Enalapril trial, a clinical trial in which more than 12,000 patients were treated with the ACE-NEP inhibitor omapatrilat, diabetics were protected from angioedema (odds ratio, 0.58; 95% CI, 0.38-0.90; $P = .014$; data from Bristol-Myers Squibb Co, New York, NY).

The data presented herein suggest that concomitant treatment with a DPPIV inhibitor might increase the risk of angioedema in ACE inhibitor–treated patients. Given the variable temporal relationship between the first use of an ACE inhibitor and the onset of angioedema, the effect of DPPIV inhibition on the risk of angioedema in ACE inhibitor–exposed patients might be difficult to discern. It is possible that pharmacologic inhibition of the enzyme will not result in the same effects as genetic deficiency. On the other hand, loss of DPPIV activity in patients with chronic rhinosinusitis leads to substance P–mediated tissue inflammation in the nasal mucosa.[30] Significantly, Ahren et al[26,27] have reported an increased risk of nasopharyngitis in phase 2 and 3 clinical trials in patients treated with a DPPIV inhibitor; it is unclear whether these patients were exposed to ACE inhibitors.

In summary, genetic DPPIV deficiency increases ACE inhibitor–induced peritracheal edema, as assessed by means of MRI, through a neurokinin receptor–dependent mechanism. Large clinical trials or pharmacoepidemiologic studies will be necessary to determine whether DPPIV inhibition increases the risk of angioedema in ACE inhibitor–treated diabetic subjects. In the meantime physicians will need to be aware of the potential for a drug-drug interaction.

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