Lactate dilates cochlear capillaries via type V fibrocyte-vessel coupling signaled by nNOS

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Dai M, Yang Y, Shi X. Lactate dilates cochlear capillaries via type V fibrocyte-vessel coupling signaled by nNOS. Am J Physiol Heart Circ Physiol 301: H1248–H1254, 2011. First published August 19, 2011; doi:10.1152/ajpheart.00315.2011.—Transduction of sound in the inner ear demands tight control over delivery of oxygen and glucose. However, the mechanisms underlying the control of regional blood flow are not yet fully understood. In this study, we report a novel local control mechanism that regulates cochlear blood flow to the stria vascularis, a high energy-consuming region of the inner ear. We found that extracellular lactate had a vasodilatory effect on the capillaries of the spiral ligament under both in vitro and in vivo conditions. The lactate, acting through monocarboxylate transporter 1 (MCT1), initiated neuronal nitric oxide (NO) synthase (nNOS) and catalyzed production of NO for the vasodilation. Blocking MCT1 with the MCT blocker, α-cyano-4-hydroxycinnamate (CHC), or a suppressing NO production with either the nonspecific inhibitor of NO synthase, N^G-nitro-L-arginine methyl ester (l-NAME), or either of two selective nNOS inhibitors, 3-bromo-7-nitroindazole or (4S)-l-citrulline-l-arginine-5-nitrate (TFA), totally abolished the lactate-induced vasodilation. Pretreatment with the selective endothelial NO synthase inhibitor, l-N^G-(1-iminoethyl)ornithine (l-NIO), eliminated the inhibition of lactate-induced vessel dilation. With immunohistochemical labeling, we found the expression of MCT1 and nNOS in capillary-coupled type V fibrocytes. The data suggest that type V fibrocytes are the source of the lactate-induced NO. Cochlear microvessel tone, regulated by lactate, is mediated by an NO-signalized coupling of fibrocytes and capillaries.

Cochlear pericytes to regulate local blood flow by contraction or relaxation (1). Moreover, fibrocytes in the superfi-0.1 to 0.3 mm) into the cochlea was made by creating a window opening over the spiral ligament after scoring a rectangle of ventral surface. To observe the blood circulation in the vessels of the spiral ligament, we used a method previously described (17, 25). In brief, a rectangular fenestration (0.2 × 0.3 mm) into the cochlea was made by creating a window opening over the spiral ligament after scoring a rectangle of scratch marks into the bone of the fourth turn. Vessels of the cochlear lateral wall were visualized by intravital microscopy through this

MATERIALS AND METHODS

Animals. Albino guinea pigs (CRL, Duncan-Hartley, both sexes, 4 to 5 wk old, 300–450 g body wt), C57BL/6J mice (4 wk old, 18–20 g body wt, Jackson) and B6.129P2-Nos3tm1Unc/J mice (4–6 wk old, 18–20 g body wt, Jackson Laboratory) were used in this study. All procedures in this study were approved by the Institutional Animal Care and Use Committee of Oregon Health and Science University.

Intravital fluorescence microscopy in vivo. The guinea pigs were anesthetized with an injection of ketamine (40 mg/kg) and xylazine (10 mg/kg) (Abbott, Chicago, IL) and were then wrapped in a heating pad with rectal temperature maintained at ~38°C. The head was fastened to a manipulator, which was heated to prevent conductive cooling. A ventrolateral surgical dissection was carried out to expose the bulla, which was then opened over its ventral surface. To observe the blood circulation in the vessels of the spiral ligament, we used a method previously described (17, 25). In brief, a rectangular fenestration (0.2 × 0.3 mm) into the cochlea was made by creating a window opening over the spiral ligament after scoring a rectangle of scratch marks into the bone of the fourth turn. Vessels of the cochlear lateral wall were visualized by intravital microscopy through this

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window. The window is referred to as the “vessel window.” A thin cover slide was used to cover the vessel window to preserve normal physiological conditions and also to have the best optical view for recording vessel images. Vessels of the spiral ligament were visualized by adjusting the optical focus. The vessels within the window were monitored with intravital video microscopy using a long-working distance objective lens [×20, 0.4 numerical aperture (NA)]. A physiological solution containing lactate (10 mM) was superfused into the cochlea through the vessel window. Capillaries of the spiral ligament were visualized using an Olympus BXFM fluorescence microscope equipped with a long distant objective (×20, 0.4 NA). The resolution of the in vivo imaging system, limited by pixel size of the imaging CCD camera, was 0.48 μm, sufficient for image analysis.

To document changes in capillary diameter, time-lapse images were recorded at 1-s intervals.

Isolation of whole mounted lateral wall tissue. The cochleae were dissected from the auditory bullae immediately after the anesthetized guinea pigs were euthanized by exsanguination. The lateral walls were carefully removed from the cochleae. The spiral ligament was isolated by detaching the stria vascularis from the cochlear lateral wall. The lateral walls were rapidly removed and transferred to a petri dish filled with a physiological solution composed of 125 mM NaCl, 3.5 mM KCl, 5 mM glucose, 10 mM HEPES, 1.3 mM CaCl2, 1.5 mM MgCl2, and 0.51 mM NaH2PO4, bubbled with 95% O2-5% CO2. The osmolarity of the solution was adjusted to 310 mosmol/l with NaCl, and the pH was adjusted to 7.4 with NaOH. All experiments were performed at 37°C using a temperature control chamber (Warner Instruments). The tissues were maintained in the physiological solution until needed.

Time-lapse microscopy in vitro. The detached spiral ligament was positioned in an eight-channel perfusion chamber (Bioscience Tool, San Diego, CA). Capillaries of the spiral ligament were visualized by differential interference contrast optics at ×400 magnification on a Nikon Eclipse E600 with a water-immersion objective (×40, 0.8 NA). Time-lapse images were recorded at 1-s intervals using a Photometrics Sensys digital camera to record the changes in capillary diameter with perfusion of a physiological solution containing 10 mM lactate. In experiments using α-cyano-4-hydroxycinnamate (CHC), N\(^2\)-nitro-L-arginine methyl ester (l-NAME, Cat No. 0665, Tocris Bioscience, Ellisville, MI), 3-bromo-7-nitroindazole (3-Br-7-NI, Cat No. 0735, Tocris Bioscience), (4S)-N-(4-amino-5-aminoethyl)aminopentyl)-N\(^=\)-nitroguanidine (TFA, Cat No. 490070, EMD Chemicals, Gibbstown, NJ), or l-N\(^5\)-(1-iminoethyl)ornithine (l-NIO) (Cat No. 0546, Tocris Bioscience), we exposed freshly isolated tissues to these chemicals for 30 min before performing time-lapse microscopy. ImageJ software was used to measure the lumen diameter at the beginning of the perfusion and at the time when the changes in diameter were maximal (1).

**Fig. 1.** A: morphology of fibrocyte- and pericyte-populated microvessels in the spiral ligament. The fibrocytes make contact with microvessels through their end feet. B: immunofluorescence shows the relative location of fibrocytes (green), pericytes (yellow), and endothelium (red) in the spiral ligament. Dil, 1,1-dioctadecyl-3,3,3,3-tetramethylindocarbocyanine perchlorate.

**Fig. 2.** Extracellular lactate induces vasodilation and increased blood flow in the cochlear lateral wall. A: cochlear vessels in a cochlear wall (vessel window) at the third turn were visualized by a fluorescence intravital microscope with a long working distance lens. White box outlines the edges of the vessel window. B: intravital fluorescence microscopy shows that vasodilation of the cochlear capillaries to 10 mM lactate is blocked by pretreatment with the monocarboxylate transporter (MCT) blocker α-cyano-4-hydroxycinnamate (CHC). Superfusion with lactate (10 mM) to the vessel window increased both blood flow (C; n = 10) and capillary diameter (D; n = 10). Pretreatment with CHC significantly attenuated both effects. Con, control; Lac, lactate. *P < 0.01; **P < 0.001.
Capillary visualization in vivo and in vitro. The cochlear capillaries were prelabeled with the fluorescent dye, 1,1-dioctadecyl-3,3,3,3-tetramethylindocarbocyanine perchlorate (DiI) (19). Before intravenous injection, the stock solution was diluted with saline to a concentration of 3 mg/ml, which was slowly administrated to the guinea pig over the course of 10 min.

NO assessment. NO production was assessed using an NO-sensitive dye, 4,5-diaminofluorescein diacetate (DAF-2DA; Cat No. 251505, EMD Chemicals), under experimental conditions as previously described (25). The detached lateral wall tissues were incubated in a petri dish with a physiological solution containing 10 μM DAF-2DA for 30 min at room temperature and washed to remove excess dye. DAF-2DA was excited at a wavelength of 480 nm on an Olympus Fluoview FV1000 confocal laser microscope, and images of emission were acquired before and after treatment with 10 mM lactate. Change in NO was assessed as the relative increase of fluorescence from the baseline intensity (ΔF/F). ΔF/F = (F1 - F0) - (F0 - F0) where F1 is the fluorescence intensity in the cells after lactate treatment, F0 is the fluorescence intensity at the beginning of the experiment, and F0 is the background fluorescence. Reverse transcription polymerase chain reaction. Total RNA from the cochlear lateral wall of three mice was separately extracted with an RNase kit (Qiagen, Valencia, CA) according to the manufacturer’s suggestions. Slc16a (MCT) family mRNA was also analyzed. One microgram of total RNA was reverse transcribed using a RETROscript kit (Ambion, Austin, TX). Conserved regions spanning introns were selected for the primers of MCTs and GAPDH. The primers used were as follows: Slc16a1 (MCT1) forward, GAGGTCTATTCACGACTTCCT, and reverse, CCAGTGCTGCTCTTGT, 220-bp product; Slc16a7 (MCT2) forward, CGTTTCCACAAACCCTTC, and reverse, CCTCCCAGATACACCCACA, 269-bp; Slc16a8 (MCT3) forward, GGCAGCCGGCTCCTTTGT, and reverse, GACGGAGCCAGTAGTGGTAA, 518-bp; Slc16a9 (MCT4) forward, ATGCCTCTAGGCACAGGACC, and reverse, GGCAGCCGGCTTGAAGTA, 229-bp product; and GAPDH forward, 5'-ATGTGTCGGTCGGATCTGAC-3', and reverse, 5'-AGACACACCTGTCCTCAGTAG-3', 132-bp product. The RT-PCR was cycled at 95°C for 2 min, up to 35 cycles at 95°C for 30 s, 60°C for 45 s, and a final 5-min extension at 72°C. The products of the reverse transcription polymerase chain reaction were visualized by agarose gel electrophoresis.

Fluorescent in situ hybridization. The animals were anesthetized with an injection of ketamine and xylazine and transcardially perfused with a solution of 4% paraformaldehyde in PBS. The cochleae were isolated from the skull and soaked in 4% paraformaldehyde for 24 h. The spiral ligaments were carefully dissected in RNase-free PBS and in situ hybridized with LNA probes (Exiqon, Woburn, MA). The tissues were dehydrated with ethanol, graded from 25 to 100%, and treated with proteinase K (10 mg/ml) for 15 min. After incubation in the prehybridization mix for 1 h (54°C, rotating), the tissues were hybridized overnight with the LNA probes. After a wash in 2× SSC for 10 min, the tissues were mounted with mounting medium with 4,6-diamidino-2-phenylindole (DAPI, Cat No. H-1500, Vector, Burlingame, CA) and observed on an Olympus IX81 inverted microscope fitted with a Fluoview FV1000 confocal laser system.

NO synthase activity assay. Cochleae were obtained from anesthetized endothelial NO synthase (eNOS) knockout mice. The spiral ligament tissues were removed and incubated in artificial labyrinth buffer for 30 min with different concentrations of the neuronal NO synthase (nNOS) inhibitor TFA. The tissues were homogenized in extraction buffer and centrifuged for 15 min at 4°C. The supernatants were collected, and 20 μl of the homogenate were incubated in 40 μl of 1 mM NADPH, 1 mM l-arginine, 1 mM CaCl2, 0.5 mM DTT and 0.1 mM (6R)-BH4 for 30 min at 37°C. The reaction was heat terminated (100°C for 1 min), and the products were centrifuged for 15 min at 4°C. The supernatants were collected, and the NO synthase (NOS) activity was measured using a Nitric Oxide Synthase Assay Kit per the manufacturer’s recommendations (Cat No. 482702, EMD Chemicals).

Immunohistochemistry. The primary antibodies used in the experiments included anti-desmin (rabbit monoclonal to desmin, Cat No. ab32362, Abcam, Cambridge, MA), anti-MCT1 (Cat No. AB3588, TAG-3’.
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Millipore, Billerica, MA), anti-S100 (Cat No. ab8330, Abcam), anti-nNOS (Cat No. 610310, BD Transduction, Lexington KY), and anti-eNOS (Cat No. ab66127, Abcam).

Secondary antibodies (Invitrogen, Carlsbad, CA) included Alexa fluor 568 conjugate goat anti-rabbit (Cat No. A11011), Alexa fluor 647 conjugate goat anti-rabbit (1:100, Cat No. A21245, Invitrogen), Alexa fluor 488 conjugate goat anti-mouse IgG (H + L) (1:100, Cat No. A11001), and Alexa fluor 647 conjugate goat anti-guinea pig (Cat No. A21450).

After the animals were euthanized, segments of the spiral ligament were removed and incubated for 30 min in a petri dish with a physiological solution containing 10 μM DAF-2DA. The tissues were fixed in 4% formaldehyde for 2 h, washed in 0.02 phosphate-buffered saline (PBS, pH 7.4) for 30 min, permeabilized in 0.5% Triton X-100 (Sigma, St. Louis, MO) for 1 h, and immunolabeled in a solution of 10% goat serum with 1% bovine albumin in 0.02 M PBS for 30 min. The specimens were incubated overnight with the primary antibody diluted in 1% BSA-PBS. The specimens were washed in 0.02 M PBS for 30 min and incubated with a secondary antibody (diluted 1:100 in 1% BSA-PBS) for 1 h. After being washed in 0.02 M PBS for 30 min, the tissues were mounted and observed on an Olympus IX81 inverted microscope fitted with a Fluoview FV1000 confocal laser system. Negative controls included tissue incubated with 1% BSA-PBS replacing the primary antibody or incubated with a blocking peptide.

Statistics

Data, presented as means ± SD, were evaluated using the Student’s t-test for comparison of two groups or ANOVA for comparisons of three or more groups. A 95% confidence level was considered statistically significant.

RESULTS

Lactate increases cochlear blood flow. To measure blood flow and capillary diameter in guinea pig cochlea in vivo, a vessel window at the third turn of the cochlea was made in a living guinea pig (as described in MATERIALS AND METHODS). An intravenous injection of Dil enabled visualization of the capillaries (Fig. 2A). A local perfusion system allowed the physiological conditions to be maintained and topical application of experimental agents and artificial perilymph. Superfusion of 10 mM lactate for 15 min significantly increased cochlear blood flow in the guinea pig (baseline blood flow was 128.3 ± 5.8 μm/s, and flow was increased ~150% with the superfusion) (Fig. 2C, n = 10). However, pretreatment with the monocarboxylate transport blocker CHC (1 mM) fully prevented this response (Fig. 2C, n = 10). As shown in Fig. 2B, the increase in cochlear blood flow induced by lactate was accompanied by an increase in capillary diameter (Δdiameter = 17.8 ± 4.87%, and initial diameter = 9.32 ± 1.16 μm, n = 10) (Fig. 2B). Consistent with the effect of CHC on cochlear blood flow in the presence of lactate, CHC pretreatment diminished the dilatory effect of lactate (Fig. 2D, n = 10).

Lactate-induced vasodilation requires MCT1. Only one subtype of MCT1 (slc16a1) was detected by agarose gel electrophoresis after 35 amplification cycles by RT-PCR (Fig. 3A). The expression of MCT1 in the spiral ligament was further confirmed by immunohistochemical labeling. MCT1 protein was expressed in the plasma membrane of type V fibrocytes (Fig. 3B), but the MCT1 immunoactivity could not be detected in the microvessels, indicating that fibrocytes are the primary cell type in the lateral wall taking up lactate.

Tests were conducted to assess the role of MCT in lactate-induced vasodilation in vitro. Spiral ligament tissues were dissected quickly and carefully in these tests. The effect of applied lactate on capillary diameter was recorded with time-lapse microscopy. ImageJ was used to assess the change in capillary diameter from the recorded images. Consistent with the results from the in vivo study, 10 mM lactate evoked dilatation of capillaries near pericytes (Δdiameter = 8.9 ± 1.9%, and initial diameter = 9.35 ± 1.41 μm, n = 24, P < 0.01). When the sample was pretreated with 1 mM CHC, a pan-specific MCT blocker, lactate-initiated vasodilation was significantly diminished (Δdiameter = 1.8 ± 2.1%, and initial diameter = 9.18 ± 0.93 μm, n = 15, P > 0.05). Blockage of the MCT mechanism with CHC attenuated lactate-induced vasodilation, consistent with the results obtained in our in vivo study.

Lactate induces NO production. In this study, we tested whether NOS activation is required for lactate-induced vasodilation of capillaries. Tissues were pretreated with the nNOS inhibitor L-NAME (10 μM) for 10 min. The results showed that pretreatment with L-NAME almost completely eliminated the vasodilative response to lactate (Fig. 4, A and B).

![Fig. 4. A: representative time-lapse images show lactate-induced change in vessel diameter with and without the nitric oxide (NO) synthase (NOS) inhibitor Nω-nitro-l-arginine methyl ester (l-NAME). White lines outline the position of the vessel wall, whereas dashed white line indicates the previous position of the vessel wall and the red line indicates the diameter of the vessel. B: mean capillary diameter is significantly increased after lactate perfusion (n = 24, *P < 0.01). In contrast, mean capillary diameter shows no change in tissues pretreated with the MCT blocker (n = 10, P > 0.05). C: confocal images show 10 mM lactate increases intracellular NO [labeled by 4,5-diaminofluorescein diacetate (DAF-2DA), green; indicated by white arrows], an effect diminished by l-NAME. D: mean values of intensity of the fluorescence, indicating NO production among different treatment groups. Mean value of NO fluorescent signal intensity is significantly increased after treatment with lactate (n = 15, *P < 0.01). In contrast, there is no change in tissues treated with the NOS blocker (n = 15, P > 0.05). FC, fibrocytes; EC, endothelial cells.](http://ajpheart.physiology.org/Downloadedfrom)
n = 15), indicating NOS contributes substantially to lactate-induced vasodilation.

To check whether lactate-induced vasodilation depends on NO production, the tissue was perfused with the NO-sensitive dye DAF-2DA (10 μM). The DAF-2DA was used as a sensor for intracellular NO in the lateral wall tissue (25). The tissues positioned in a perfusion chamber were observed on an inverted Olympus Fluoview FV1000 confocal laser microscope system. The application of lactate increased the fluorescent signal for NO in the capillary wall and in type V fibrocytes (Fig. 4C, n = 10). NO production by lactate was attenuated in the l-NAME-pretreated tissue (Fig. 4, C and D).

Lactate-induced increase in NO production via activation of nNOS. Neuronal NOS (nNOS) and endothelial NOS (eNOS) catalyze synthesis of NO from L-arginine in neurons and endothelial cells. Immunostaining showed that both isoforms of eNOS and nNOS were present in the spiral ligament (Fig. 5A). The results revealed that eNOS was selectively expressed in vascular endothelium (Fig. 5A), whereas nNOS was selectively expressed in fibrocytes (Fig. 5A). Selective expression of nNOS in fibrocytes was further confirmed by a whole mount fluorescent in situ hybridization experiment (Fig. 5B).

The results, shown in Fig. 4, implicate NOS in vessel dilation by lactate but do not address the type of NOS involved. In this study, TFA (a potent nNOS inhibitor), 3-Br-7-NI (a relatively selective nNOS inhibitor), and L-NIO (a relatively selective eNOS inhibitor) were used to intervene with lactate-induced changes. Lactate-induced vasodilation was inhibited...
by pretreatment with 10 μM 3-Br-7-NI (Fig. 5C, Δdiameter = $2.3 \pm 3.1\%$, and initial diameter = $9.41 \pm 1.33 \mu m$, $n = 15$, $P > 0.05$) and 10 μM TFA (Fig. 5C, Δdiameter = $0.7 \pm 3.9\%$, and initial diameter = $9.08 \pm 1.06 \mu m$, $n = 15$, $P > 0.05$) but was unaffected by pretreatment with 10 μM L-NIO (Fig. 5C, Δdiameter = $7.4 \pm 3.2\%$, and initial diameter = $9.26 \pm 1.17 \mu m$, $n = 15$, $P < 0.01$). The findings suggest that extracellular lactate likely causes vasodilation through a nNOS signal pathway.

**DISCUSSION**

The cochlea has rapidly changing metabolic requirements, and fast-acting mechanisms are needed to adjust vessel tone. Although little is known about how microvascular blood flow in the cochlea is regulated, there is increasing evidence that vasoactive agents are involved in the fine control over capillaries in the lateral wall. Lactate acts as a dynamic vasoactive agent in retinal and brain microvasculature (12, 30), indicating that lactate is the bridging agent which links metabolic need to local blood flow. In the present investigation of cochlear capillaries, lactate modulation of vessel diameter was demonstrated both in vitro and in vivo. This is the first demonstration that lactate causes a significant increase of local blood flow in the cochlea by affecting dilation of microvessels. The lactate-induced vasodilation requires the activation of nNOS in fibrocytes.

MCTs facilitate transport and cellular uptake of lactate (14). Our results show that MCTs play a major role in lactate-induced vasodilation, as inhibition of CHC significantly diminishes vasodilation. Of the fourteen MCTs identified (5), only MCT1-MCT4 are shown to catalyze proton-coupled transport of lactate (2, 6, 29). Our PCR and immunofluorescence results indicate that MCT1 is the predominant subtype expressed in cochlear lateral wall tissue. More importantly, the expression of MCT1 is localized in the plasma membranes of fibrocytes, whereas the expression of MCT1 is virtually undetectable in microvessels. This suggests that the locus of lactate vasoactivity is the MCT1 expressed in fibrocytes.

Since NO has been shown to be essential for lactate-induced vasodilation in various other organs (12), it is reasonable to assume that NO also plays a role in lactate-induced cochlear vasodilation. In agreement with studies in other organs, lactate-induced vasodilation in the cochlea was almost completely blocked by L-NAME, indicating NO is the major mediator of lactate-induced vasodilation in cochlear microvessels. Two isoforms of calcium-dependent constitutive NOS are detected in the spiral ligament: eNOS is mainly expressed by vascular endothelium, whereas nNOS expression is localized in fibrocytes. Specific blocking of nNOS and eNOS enabled identifying nNOS as the source of the NO in lactate-induced cochlear vasodilation. Pretreatment with a selective nNOS inhibitor significantly reduced NO production and inhibited vasodilation in response to extracellular lactate. On the other hand, vasodilation caused by lactate was marginally changed with the suppression of eNOS from pretreatment of tissues with the selective eNOS inhibitor L-NIO. Since MCT1 is also expressed in fibrocytes and the fibrocytes are in close contact with endothelial cells and pericytes, we speculate that extracellular lactate activates nNOS in fibrocytes through MCT1. The direct measurement of lactate-initiated NO production in fibrocytes confirmed the hypothesis. A significant increase in DAF-2DA fluorescence (an NO indicator) in fibrocytes is detected after stimulation with lactate.

Blood supply for the cochlea is supplied by two microvessel networks located in the stria vascularis and spiral ligament. Capillaries of the spiral ligament, arteriovenular anastomosing vessels, are considered to be the primary network regulating cochlear blood flow, whereas the capillaries of the stria vascularis are considered secondary. Our previous studies showed that type V fibrocytes in contact with microvessels nearby in the superstrial region form fibrovascular-coupling units. We speculate that this fibrovascular-coupling unit, similar to neurovascular coupling units in the brain and retina, functionally regulates local blood flow to meet the local metabolic demand (3, 8, 15, 31). As we propose in the working model of Fig. 6, increased cochlear metabolism (e.g., under sound stimulation) also increases glycolysis and lactate production. Increased lactate acts as a signal that increases local blood flow by regulating the fibrovascular-coupling unit.

In summary, the present study provides the first direct evidence that lactate causes dilation of cochlear capillaries. The uptake of lactate by fibrocytes through an MCT1 transport pathway leads to the activation of nNOS and the production of NO, which induces vasodilation.
GRANTS
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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

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