Localized vs. systemic inflammation in guinea pigs: a role for prostaglandins at distinct points of the fever induction pathways?

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Localized vs. systemic inflammation in guinea pigs: a role for prostaglandins at distinct points of the fever induction pathways? Am J Physiol Regul Integr Comp Physiol 289: R340–R347, 2005. First published April 14, 2005; doi:10.1152/ajpregu.00104.2005.—In guinea pigs, dose-dependent febrile responses were induced by injection of a high (100 μg/kg) or a low (10 μg/kg) dose of bacterial lipopolysaccharide (LPS) into artificial subcutaneously implanted Teflon chambers. Both LPS doses further induced a pronounced formation of prostaglandin E2 (PGE2) at the site of localized subcutaneous inflammation. Administration of diclofenac, a nonselective cyclooxygenase (COX) inhibitor, at different doses (5, 50, 500, or 5,000 μg/kg) attenuated or abrogated LPS-induced fever and inhibited LPS-induced local PGE2 formation (5 or 500 μg/kg diclofenac). Even the lowest dose of diclofenac (5 μg/kg) attenuated fever in response to 10 μg/kg LPS, but only when administered directly into the subcutaneous chamber, and not into the site contralateral to the chamber. This observation indicated that a localized formation of PGE2 at the site of inflammation mediated a portion of the febrile response, which was induced by injection of 10 μg/kg LPS into the subcutaneous chamber. Further support for this hypothesis derived from the observation that we failed to detect elevated amounts of COX-2 mRNA in the brain of guinea pigs injected subcutaneously with 10 μg/kg LPS, whereas subcutaneous injections of 100 or 500 μg/kg LPS, as well as systemic injections of LPS (intraperitoneal routes), readily caused expression of the COX-2 gene in the guinea pig brain, as demonstrated by in situ hybridization. Therefore, fever in response to subcutaneous injection of 10 μg/kg LPS may, in part, have been evoked by a neural, rather than a humoral, pathway from the local site of inflammation to the brain.

lipopolysaccharide; febrile response; prostaglandin E2; cyclooxygenase-2; immune system-to-brain communication

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the nonselective COX inhibitor diclofenac into the subcutaneous chamber at the rather high dose of 5 mg/kg abolished LPS-induced fever in this specific experimental model (29). This high dose of diclofenac might, however, have depressed the formation of prostaglandins also at other sites, for example, in the brain.

The aim of the present study was therefore to obtain further evidence for the participation of locally produced prostaglandins in the manifestation of fever during localized subcutaneous inflammation. For this purpose, we progressively reduced the dose of diclofenac that was injected along with LPS into the subcutaneous chamber and measured the resulting fever responses. We further tested the capacity of diclofenac to block the LPS-induced local formation of prostaglandin E₂ (PGE₂), which is regarded as a critical endogenous mediator of fever. Finally, for the first time in the guinea pig, we studied the expression of COX-2 mRNA in the brain during localized, as opposed to systemic, LPS-induced inflammation.

MATERIALS AND METHODS

Animals

Male guinea pigs (Cavia aperea porcellus, 390–430 g body wt on the day of surgery) were housed in individual cages at 22°C and exposed to a 12:12-h light-dark cycle (lights off at 7 PM). The animals had access to food and water ad libitum. Twice a week the reservoirs were filled with fresh pellet food and water, and at the same time the cages were changed. At ~10 days before the fever experiment, the animals were prepared surgically (see below) and habituated to the handling procedures at least twice before the experiment. The national guidelines for experiments with vertebrate animals were followed, and approval for the experimental protocols was obtained from the local ethics committee (GI 18/2-42/00).

Surgery

At ~10 days before the experiment, the animals were chronically implanted with artificial subcutaneous Teflon (polytetrafluoroethene) chambers equipped with catheters for injection of drugs and collection of lavage and radio transmitters for measurement of body temperature.

Briefly, the guinea pigs were anesthetized with 100 mg/kg ketamine hydrochloride (Pharmacia Upjohn, Erlangen, Germany) and 0.25 mg/kg medetomidine hydrochloride (Pfizer, Karlsruhe, Germany). The Teflon chambers were implanted into subcutaneous cavities, which were formed with a cylindrical Plexiglas stick after a cutaneous incision. The cavities that remained after removal of the Plexiglas stick had about the same diameter and size as the artificial subcutaneous chamber, which was open at both ends. The open sides of the cylindrical chambers (10 mm ID) had close contact with the skin tissue. The subcutaneous chamber was placed laterally to the dorsal midline and caudally to the scapulae of the anesthetized guinea pigs. The chambers were equipped with catheters for administration of drugs and sampling of lavage fluid that were tunneled subcutaneously to the interscapular region of the back and sealed by heating. Then the skin was closed with sutures (for details about size and shape of the subcutaneous chambers see Refs. 38 and 39). After surgical placement of the subcutaneous chamber, a biotelemetry transmitter was implanted intraperitoneally for measurement of core temperature.

For experiment 3, some guinea pigs were implanted with intra-articular, instead of subcutaneous, chambers (for details about the intra-articular catheter see Refs. 29 and 30). All implanted materials were sterilized, and all the surgical procedures were conducted under aseptic conditions.

Substances

Bacterial LPS (derived from Escherichia coli, O111:B4; Sigma Chemical, St. Louis, MO) was suspended in sterile pyrogen-free 9.9% saline at 100 μg/ml (high dose) or 10 μg/ml (low dose). Doses of 100 or 10 μg/kg were used for injections into the subcutaneous chamber. In experiment 3, some animals received systemic injections of LPS at 10 μg/kg (intra-arterial route of administration; prepared from a 10 μg/ml LPS solution) or 30 μg/kg (intraperitoneal route of administration; prepared from a 30 μg/ml LPS solution). Equivalent volumes of the vehicle were injected in control groups. All LPS doses were chosen according to previous studies from this laboratory (11, 29–32, 34).

Diclofenac sodium (Calbiochem, La Jolla, CA) was dissolved at 5,000, 500, 50, or 5 μg/ml in vehicle, which consisted of 95% sterile saline and 5% ethanol. In these solutions, diclofenac was injected into the subcutaneous chamber, together with LPS or an equivalent volume of solvent (0.9% saline) at 5,000, 500, 50, or 5 μg/kg, corresponding to a consistent injection volume of 1 ml/kg. Control groups were injected with an equivalent volume of vehicle (1 ml vehicle/kg) together with LPS or saline.

Experimental Protocols

On the day of the experiment, each previously implanted subcutaneous chamber was tested for accumulation of fluid in the chamber by aspiration with a syringe through the catheter. The experiment was performed only if there was <0.1 ml of fluid in the syringe.

Experiment 1: dose-dependent attenuation of LPS fever by coinjection of diclofenac. The influence of four doses of diclofenac (5,000, 500, 50, or 5 μg/kg) injected into the subcutaneous chamber along with LPS (100 or 10 μg/kg) or with an equivalent volume of solvent on the manifestation of a febrile response was studied. In an additional control experiment, the lowest dose of diclofenac or solvent was injected subcutaneously into the site contralateral to the chamber simultaneously with administration of 10 μg/kg LPS or saline into the subcutaneous chamber. Each of the treatment groups consisted of five or six animals.

Experiment 2: measurement of PGE₂ in lavage fluid of the subcutaneous chamber. In separate experiments, we collected lavage fluid from the subcutaneous chamber 120 min after the respective injections to study a localized formation of PGE₂ and the influence of diclofenac on LPS-induced PGE₂ production. This time point was chosen according to data from the literature on peripheral LPS-induced formation of PGE₂ (36) and according to our own pilot measurements showing consistently elevated PGE₂ concentrations in lavage fluid 2 h after LPS administration. Localized PGE₂ formation was measured in response to both administered doses of LPS or saline along with solvent or with a high (500 μg/kg) or a low (5 μg/kg) dose of diclofenac.

To collect lavage fluid from the artificial subcutaneous chamber, 1 ml of sterile saline was slowly injected into the chamber through the catheter, left in the chamber for ~30 s, withdrawn again into a sterile syringe, and immediately centrifuged, so that a clear supernatant without cells was obtained. Thereafter, the catheter was flushed with a small volume (0.1 ml) of sterile pyrogen-free saline and closed by heating. The supernatant was stored at ~70°C for later determination of PGE₂.

Experiment 3: detection of COX-2 mRNA in the guinea pig brain during systemic or localized inflammation. Using radioactive in situ hybridization (see below), we studied the expression of COX-2 in the guinea pig brain during systemic or localized inflammation induced by intra-arterial (10 μg/kg, n = 2) or intraperitoneal (30 μg/kg, n = 2) injections of LPS vs. injections of LPS (100 or 10 μg/kg, n = 3 for each LPS dose) into the artificial subcutaneous chambers. Five control animals were injected with 0.9% saline instead of LPS: two intra-arterially, one intraperitoneally, and two subcutaneously. COX-2 expression was determined 180 min after the respective injections. This time point was chosen according to our own pilot experiment in guinea pigs and according to published studies on LPS-induced COX-2 mRNA expression in the rat or mouse brain (5–7, 25).
Measurement of Body Temperature

Intraperitoneally implanted (see above) battery-operated biotelemetry transmitters (VM-FH disks or PDT-4000 E-mitter, Mini-Mitter, Sunriver, OR) were used to measure core temperature. Output (frequency in Hz) was monitored with an antenna placed under each cage (RA 1000 or ER-4000 radio receivers, Mini-Mitter). A data acquisition system (Vital View, Mini-Mitter) was used for automatic control of data collection and analysis. Body temperature was monitored and recorded at 5-min intervals. For analysis and graphical documentation, temperature data collected at 15-min intervals were used.

PGE₂ Assay

PGE₂ in the collected lavage fluid was determined by use of a commercially available enzyme immunoassay (R & D Systems, Wiesbaden, Germany). The assay is based on the competitive binding technique in which PGE₂ in a sample competes with a fixed amount of alkaline phosphatase-labeled PGE₂ for sites on a mouse monoclonal antibody. During incubation, the mouse monoclonal antibody was bound to a goat anti-mouse antibody that coated the wells of a microplate. After the sample was washed once to remove excess conjugate and unbound sample, a substrate solution was added to the wells for determination of the bound enzyme activity. Immediately after color development, the absorbance was read at 405 nm on a microplate reader (Digiscan, Assys HighTech, Eugendorf, Austria). The color intensity inversely correlated with the PGE₂ concentration in the sample. According to the manufacturer’s product information, the sensitivity of the PGE₂ assay was ~35 pg/ml.

COX-2 In Situ Hybridization

Animals were decapitated 180 min after local or systemic injections of LPS or 0.9% NaCl (Controls), and the brains were removed quickly, frozen on dry ice, and stored at −70°C until further use. For COX-2 mRNA hybridization, coronal cryostat sections (20 μm; model HM 500-O, Microm, Walldorf, Germany) were obtained from brain regions containing the subforminal organ (SFO) and the vascular organ of the lamina terminalis, both of which are implicated in fever (34, 37), as well as other hypothalamic and extrahypothalamic brain areas. Sections were mounted and processed as previously described (1) and then hybridized with oligodeoxynucleotide probes complementary to nt 932 to 888, nt 1049 to 1005, and nt 1321 to 1277 of the guinea pig COX-2 cDNA (GenBank accession no. Y07896.1). Specificity of probe sequences for complementarity exclusively with COX-2 cDNA was checked vs. GenBank by blastN (National Center for Biotechnology Information) and sequence alignments (ClustalW 1.8, National Center for Biotechnology Information) with published partial sequence sets of guinea pig COX-1 cDNA (GenBank accession nos. AF757362 and AB054840). The probe labeling and high-stringency hybridization procedure followed a recently published protocol (1) using 50 μl/sec of an equimolar mixture with the three oligodeoxynucleotide probes and a final probe concentration of 7.5–10 × 10⁵ cpm/μl hybridization buffer. For autoradiographical detection, X-ray films (Kodak Biomax MR) were exposed to hybridized sections for 10–17 days.

Evaluation and Statistics

Body temperature changes in response to injections of LPS or saline combined with diclofenac or solvent of the different experimental groups were plotted against time and expressed as means ± SE at each time point. Changes of abdominal temperatures between groups were compared by two-way repeated-measures ANOVA followed by an all-pairwise Bonferroni’s multiple comparison post hoc test (Sigmastat/Sigmastat analysis software, Jandel Scientific, SPSS Science Software, Erkrath, Germany). Concentrations of PGE₂ were compared between the experimental groups by one-way ANOVA followed by Scheffe’s post hoc test (StatView, Abacus Concepts, Berkeley, CA). Statistical analyses resulting in P < 0.05 were considered significant.

RESULTS

Experiment 1: Dose-Dependent Attenuation of LPS-Induced Fever by Coinjection of Diclofenac

The effects of injections of 100 μg/kg LPS into the subcutaneous chamber along with solvent (L100 + solvent) or different doses of diclofenac (5 and 50 μg/kg diclofenac (L100 + D5 and L100 + D50, respectively; top) and 500 and 5,000 μg/kg diclofenac (L100 + D500 and L100 + D5000, respectively; bottom). Tᵢ, initial (time 0, i.e., before injection) temperature; n, number of animals. Dashed horizontal lines in Figs. 1–3 indicate mean baseline temperature that was calculated from all temperatures measured within the 2 h before injection.

Fig. 1. Changes in abdominal temperatures [body (core) temperature (Tb)] of 5 groups of guinea pigs injected subcutaneously with 100 μg/kg LPS along with solvent (L100 + solvent) or different doses of diclofenac [5 and 50 μg/kg diclofenac (L100 + D5 and L100 + D50, respectively; top) and 500 and 5,000 μg/kg diclofenac (L100 + D500 and L100 + D5000, respectively; bottom)]. Tb, initial (time 0, i.e., before injection) temperature; n, number of animals. Dashed horizontal lines in Figs. 1–3 indicate mean baseline temperature that was calculated from all temperatures measured within the 2 h before injection.

At 100 μg/kg, LPS elicited two clearly distinct phases of fever, lasting 90 and 270 min, respectively. Treatment with 5 or 50 μg/kg diclofenac slightly delayed the onset of fever and reduced the magnitude, but not the course, of both fever phases (Fig. 1, top). At 30–150 min after injection, both doses of diclofenac significantly reduced fever in response to injections of 100 μg/kg LPS into the subcutaneous chamber (P < 0.05, 2-way repeated-measures ANOVA and Bonferroni’s multiple comparison post hoc test).

Treatment with 500 or 5,000 μg/kg diclofenac depressed both fever phases (Fig. 1, bottom; for 500 μg/kg, P < 0.001 from 15 to 270 min after injection; for 5,000 μg/kg, P < 0.001 from 15 to 360 min after injection; 2-way ANOVA and Bonferroni’s post hoc test). Subcutaneous treatment with 5,000...


µg/kg diclofenac along with 100 µg/kg LPS even induced a hypothermic response. Pronounced alterations of abdominal temperatures were not observed in any of the control groups injected with saline instead of LPS (not shown).

Identical experiments were also performed with the low LPS dose (10 µg/kg), and the results are summarized in Fig. 2.

Again, we observed a dose-dependent attenuation of fever by coinjections of diclofenac. When injected with LPS into the subcutaneous chamber, even the lowest dose of diclofenac (5 µg/kg) significantly reduced the mean LPS-induced increase of abdominal temperature from 165 to 360 min after the injection (Fig. 2, top; P < 0.05, 2-way repeated-measures ANOVA and Bonferroni’s multiple comparison post hoc test). Diclofenac at 50 µg/kg significantly reduced fever from 120 to 360 min after injection (P < 0.01). The initial phase of fever induced by the lower LPS dose was, however, evidently not affected by treatment with 5 or 50 µg/kg diclofenac. Again the higher doses of diclofenac (500 and 5000 µg/kg; Fig. 2, bottom) caused a more pronounced depression of fever. The onset of fever was delayed by 60 min in guinea pigs injected with 500 µg/kg diclofenac along with 10 µg/kg LPS into the subcutaneous chamber. The highest dose of the nonselective COX inhibitor even induced a slight hypothermia. The antipyretic effects of 500 or 5000 µg/kg diclofenac were significant from 30 to 360 min after injection (P < 0.001, 2-way ANOVA and Bonferroni’s post hoc test).

Because a systemic action of diclofenac by entry of the drug from the subcutaneous chamber into the blood could not be ruled out, we tested whether a subcutaneous injection of the lowest dose of the COX inhibitor reduced fever in response to 10 µg/kg LPS also when injected subcutaneously into the site contralateral to the chamber. The result of this experiment is shown in Fig. 3.

Injections of 10 µg/kg LPS into the subcutaneous chamber resulted in identical changes of abdominal temperature in guinea pigs, irrespective of simultaneous administration of 5 µg/kg diclofenac or an equivalent volume of solvent into the contralateral site of the chamber position (Fig. 3, top). This result indicates that subcutaneous injections of 5 µg/kg diclofenac may have no substantial systemic effect with regard to the manifestation of fever under these specific conditions.

Experiment 2: Measurement of PGE2 in Lavage Fluid of the Subcutaneous Chamber

The results of the PGE2 measurements in lavage collected 120 min after the different treatments are summarized in Fig. 4.

Both doses of LPS injected into the chamber caused a significant rise of PGE2 in lavage fluid, which tended to be more pronounced in response to the high LPS dose (Fig. 4, top left). An almost complete suppression of LPS-induced local formation of PGE2 was achieved by injections of a high or low dose of diclofenac in both LPS-treated groups (Fig. 4, top right and bottom left). The moderate levels of PGE2, which were present in the control group, tended to be attenuated by treatment with diclofenac (Fig. 4, bottom right).

Fig. 3. Top: Changes in abdominal temperatures of guinea pigs injected with 10 µg/kg LPS into the subcutaneous chamber and 5 µg/kg diclofenac or solvent subcutaneously into the site contralateral (cl) to the chamber (L10 + solvent cl and L10 + D5 cl, respectively). Bottom: Changes in abdominal temperatures of guinea pigs injected with saline into the subcutaneous chamber and 5 µg/kg diclofenac or solvent subcutaneously into the site contralateral to the chamber position (NaCl + solvent cl and NaCl + D5 cl, respectively). See Fig. 1 legend for details.
and in brain vessels distributed throughout the entire guinea pig brain, COX-2 mRNA signals are mainly associated with blood vessels in animals treated intra-arterially or intra-peritoneally with LPS. A similar observation was made in the guinea pig brain. Brain sections containing the SFO of the different LPS-treated animals and of a control are shown in Fig. 5. It thus seems that, during a moderate localized inflammatory response induced by injection of 10 μg/kg LPS into the subcutaneous chamber, a pronounced COX-2 induction in the guinea pig brain is absent, despite the manifestation of a moderate fever (Fig. 2).

DISCUSSION

Using the subcutaneous chamber as a model to induce a localized inflammatory response, we previously (30) analyzed the febrile responses of guinea pigs to injections of a high (100 μg/kg) or a low (10 μg/kg) dose of LPS into the chamber. In this study (30), we tested the effects of administration of the local anesthetic ropivacaine, along with LPS, into the subcutaneous chamber. Fever in response to the low, as opposed to the high, LPS dose was attenuated by treatment with the local anesthetic. A systemic action of ropivacaine could be ruled out, because when injected subcutaneously on the contralateral side of the animal in relation to the chamber at the same dose, it failed to alter fever induced by the low dose of LPS (30). This result suggests that local signals that were blocked by the local anesthetic in the chamber might have participated in the transmission of febrile signals from a localized site of peripheral inflammation, in this case, the subcutaneous chamber, to parts of the brain that are involved in the generation of fever. One local effect of ropivacaine was reduced formation of LPS-induced TNF at the site of inflammation (30). In another study, we therefore successfully neutralized the locally produced TNF by a synthetic TNF-binding protein and observed a reduction of the late phase of fever in response to injection of the low LPS dose into the subcutaneous chamber (29). In response to the high LPS dose, neither the local anesthetic nor treatment with TNF-binding protein had an effect on fever. We speculated that, in the case of the high LPS dose, humoral signals (i.e., IL-6) entering the systemic circulation from the chamber in sufficient amounts could totally override the local components for the induction of fever.

An obvious effect of the local anesthetic is a silencing of local afferent nerve fibers. Inflammation leads to the release of prostanoids, namely, PGE2, which sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity (21). It was therefore tempting to speculate that a peripheral, localized formation of PGE2 might also play a role in the manifestation of fever that develops in response to injections of LPS into the subcutaneous chamber, perhaps via stimulation of afferent nerve fibers. The results of the present study provide modest evidence for such a hypothesis. We clearly demonstrated a localized formation of PGE2 at the subcutaneous site of inflammation that could be blocked effectively even by the lowest tested dose of the nonselective COX inhibitor diclofenac (5 μg/kg) when injected into the chamber together with LPS. We further observed a dose-dependent attenuation or complete suppression of fever in this experimental model by local treatment with diclofenac. We were especially interested in the effect of a low dose of the COX inhibitor on fever in response to subcutaneous injections of 10 μg/kg LPS because of the previously described effect of the local anesthetic (30) and because of the almost complete lack of brain activation by circulating cytokines under these experimental conditions (34).
Indeed, a systemic effect of the lowest applied dose of diclofenac could be ruled out, because an injection of this dose of the COX inhibitor into the subcutaneous tissue contralateral to the chamber position did not attenuate fever (Fig. 3). Nevertheless, the following question arises: How might peripherally (locally) produced PGE$_2$ contribute to the manifestation of fever? On the one hand, the effects of PGE$_2$ could be mediated locally at the site of inflammation. From the skin, a predominant input of signals from cold fibers into the thermoregulatory system shows characteristic static and dynamic discharge patterns (4). An activation of cutaneous cold receptors results in characteristic cold defense reactions (vasoconstrictions and increased heat production), responses that are also observed during a febrile rise of body temperature. Interestingly, a preliminary report has been published (20) showing a specific activation of peripheral cold-sensitive neurons by PGE$_2$. However, the activation of cold defense reactions is usually observed in the rising phase of fever, which was obviously unimpaired by treatment with the lowest dose of diclofenac (Fig. 2). Consistent with the rapid onset of cold defense responses during the initial phase of fever, it has been reported that neural signaling mechanisms are mostly involved in the early phases of a given febrile response (26). According to the data presented, we must admit that the local formation of PGE$_2$ in our model has just a moderate effect and exclusively contributes to the maintenance of fever. This becomes obvious by the fact that fever in response to the low LPS dose was not attenuated within the first 2 h, despite the absence of PGE$_2$ in the chamber at 120 min under the influence of 5 g/kg diclofenac.

It thus seems difficult to explain how the rapid onset and the manifestation of the first 2 h of fever are mediated in our experimental model of a moderate local inflammation (subcutaneous injection of the low LPS dose). A possible mechanism for induction of fever after intraperitoneal injection of a low dose of LPS in guinea pigs has been suggested recently (3). The monophasic fever that develops under this condition seems to be initiated by an $\alpha_1$-adrenoreceptor-mediated and PGE$_2$-independent mechanism within the preoptic-anterior hypothalamic area in response to vagally transmitted signals of peripheral LPS. According to this study, the later phase of fever is mediated by an $\alpha_2$-adrenoreceptor-mediated and PGE$_2$-dependent mechanism (3). Perhaps a similar mechanism operated in our experimental model.

With regard to our experiments in which we used the high LPS dose (100 g/kg) for injections into the subcutaneous
chamber, it seems that distinct mechanisms were activated to establish a febrile response. The fever, in this case, was biphasic. The shape of the fever curve resembled a curve after systemic treatment with LPS (32, 34). Although the local formation of PGE2 within the subcutaneous chamber was similar in response to both LPS doses (Fig. 4), there was a pronounced difference in the expression of COX-2 in the brain, which is regarded as critical for the manifestation of fever by several authors (7, 12, 15, 18, 24, 39). Injections of the high (as opposed to the low) dose of LPS into the subcutaneous chamber caused expression of COX-2 in the guinea pig brain, which may have contributed to the development of the very pronounced second fever phase. Consistent with this observation, we previously reported that humoral mechanisms cause direct brain activation under these specific experimental conditions (34).

In conclusion, the mechanisms for the manifestation of fever in response to a localized peripheral inflammatory stimulus seem to depend on the strength of the inflammatory stimulus. A local formation of PGE2 at the peripheral site of inflammation seems to participate in the maintenance of fever in response to a moderate inflammatory stimulus. If the inflammatory stimulus is strong enough to induce sufficient amounts of humoral mediators, such as cytokines, prostaglandins, or LPS itself (2, 13, 16, 19, 27, 28, 33, 35), expression of COX-2 is induced in the brain and contributes to the maintenance of fever under these conditions.

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