Elevated ambient glucose induces acute inflammatory events in the microvasculature: effects of insulin

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Booth, Gregory, Timothy J. Stalker, Allan M. Lefer, and Rosario Scalia. Elevated ambient glucose induces acute inflammatory events in the microvasculature: effects of insulin. Am J Physiol Endocrinol Metab 280: E848–E856, 2001.—We employed intravital microscopy of the rat mesenteric microvasculature to study the effects of local hyperglycemia on leukocyte-endothelial cell interactions. Intraperitoneal injection of 6, 12.5, and 25 mmol/l D-glucose to the rat significantly and time-dependently increased leukocyte rolling and leukocyte adherence in, and leukocyte transmigration through mesenteric venules compared with control rats injected with Krebs-Henseleit (K-H) solution alone or given K-H solution alone or 25 mmol/l L-glucose intraperitoneally. The response elicited by D-glucose was associated with significant attenuation of endothelial nitric oxide (NO) release, as demonstrated by direct measurement of NO release in inferior vena cavae segments isolated from rats exposed to 25 mmol/l D-glucose for 4 h (P < 0.01 vs. vena caval segments from control rats). Local application of 0.05 U/min insulin for 90 min significantly attenuated glucose-induced leukocyte rolling, adherence, and migration (P < 0.01 vs. 25 mmol/l D-glucose alone). Immunohistochemical localization of P-selectin expressed on endothelial surface was significantly increased 4 h after exposure of the mesenteric tissue to high ambient glucose (P < 0.01 vs. ileal venules from rats injected with K-H solution alone or 25 mmol/l D-glucose). Insulin markedly inhibited endothelial cell surface expression of P-selectin in ileal venules exposed to elevated ambient glucose in vivo (P < 0.01 vs. control rats injected with 25 mmol/l D-glucose). These data demonstrate that acute increases in ambient glucose comparable to those seen in diabetic patients are able to initiate an inflammatory response in the microcirculation. This inflammatory response to glucose is associated with upregulation of the endothelial cell adhesion molecule P-selectin and can be blocked by local application of insulin.

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Experimental Protocol

We used male Sprague-Dawley rats weighing 250–270 g. Leukocyte-endothelium interactions were studied in rat mesenteric venules 12 h after exposure of the mesentery to 6, 12.5, and 25 mmol/l D-glucose. Rats were randomly divided into one of the following experimental groups: 1) control rats intraperitoneally injected with 0.9% NaCl, 2) control rats injected with 25 mmol/l D-glucose intraperitoneally, 3) rats injected with 6 mmol/l D-glucose, 4) rats injected with 12.5 mmol/l D-glucose, and 5) rats injected with 25 mmol/l D-glucose. The effects of 0.05 U/min insulin on leukocyte-endothelium interaction were also tested in rat mesenteries exposed to 25 mmol/l D-glucose for a 12-h period.

In an additional set of experiments, the time course of glucose-induced leukocyte-endothelium interactions were investigated at 2, 4, and 12 h after a single intraperitoneal administration of 25 mmol/l D-glucose.

D-Glucose (Sigma Chemicals, St. Louis, MO) was freshly prepared daily in sterile 0.9% NaCl. A total volume of 2.5 ml was injected into each rat intraperitoneally. L-Glucose (Sigma) was used at a concentration of 25 mmol/l as a control to exclude nonspecific osmolarity effects of D-glucose. Porcine insulin was used at a concentration of 25 mmol/l as control in mmol/l: 118 NaCl, 4.74 KCl, 2.45 CaCl₂, 1.19 KH₂PO₄, and mesentery were superfused throughout the experiment in an oxygenated K-H solution containing (in mmol/l): 118 NaCl, 4.74 KCl, 2.45 CaCl₂, 1.19 KH₂PO₄, 1.19 MgSO₄, 12.5 NaHCO₃) warmed to 37°C and bubbled with 95% N₂-5% CO₂. A Microphot microscope and a ×40 water immersion lens (Nikon, Tokyo, Japan) were used to visualize the mesenteric microcirculation and the mesenteric tissue. The image was projected by a high-resolution color video monitor (Multiscan 200-sf), and the image was analyzed using computerized imaging software (Phase 3 Image System, Media Cybernetics) on a Pentium-based IBM-compatible computer (Micron Millenia Mxe, Micron Electronics). Red blood cell velocity was determined on-line using an optical Doppler velocimeter (6) obtained from the Microcirculation Research Institute (College Station, TX). After a 20- to 30-min stabilization period, a 30- to 50-μm-diameter post-capillary venule was chosen for observation. Video recordings were made at 30, 60, 90, and 120 min for quantification of leukocyte rolling, adherence, and transmigration. Leukocyte rolling is expressed as the number of cells moving past a designated point per minute (i.e., leukocyte flux); adherence is expressed as the number of leukocytes adhering to the endothelium per 100 μm of vessel length; transmigrated leukocytes were determined in an area covering a distance of 10 μm in either direction from the vessel wall. The number of extravasated leukocytes was counted and normalized with respect to the immediate perivascular area surrounding the venule (10 μm from the endothelium × 100 μm long along the venule). Red blood cell velocity (V_rbc) and venular diameter (D) were used to calculate venular wall shear rate (g) employing the formula g = 8 × (V_mean/D); V_mean = V_rbc/1.6, where V = velocity, and D = diameter (14).

Immunohistochemistry

Immunohistochemical localization of P-selectin was determined after intravital microscopy was completed, as previously described (37). Both the superior mesenteric artery and superior mesenteric vein were then rapidly cannulated for perfusion fixation of the small bowel. The ileum was first washed free of blood by perfusion with K-H buffer and then fixed in situ with iced 4% paraformaldehyde. A 3- to 4-cm-long segment of ileum was isolated, cut into rings, and dehydrated using graded acetone washes at 4°C. Tissue sections were embedded in plastic (Immunobond, Polysciences, Warrington, PA), and 4-μm-thick sections were cut and transferred to Vectabond-coated slides (Vector Laboratories, Burlingame, CA).

Immunohistochemical localization of P-selectin was accomplished using the avidin-biotin-immunoperoxidase technique (Vectastain ABC Reagent, Vector Laboratories) (46). Tissue sections were incubated with the primary antibody directed against P-selectin (PB1.3) at a dilution of 1:100 for 24 h. The tissue was then incubated with the biotinylated secondary antibody, and the peroxidase staining was carried out using 3,3’-diaminobenzidine. Control preparations consisted of omission of the primary antibody or omission of the secondary antibody. Expression of P-selectin was determined by microscopic observation of the brown peroxidase reaction product on the venular endothelium of the tissue sections. Positive staining was defined as a venule displaying brown reaction product on >50% of the circumference of its endothelium. Nine sections were studied from each rat, 50 venules per tissue section were examined, and the percentage of positive staining venules was tallied.

Quantification of NO released from isolated vena caval segments. We used freshly isolated inferior vena cava (IVC) segments as the source of primary endothelial cells. IVCs were rapidly isolated from glucose-injected rats at 4 h postinjection. Isolated vein segments were immersed into warm, oxygenated K-H solution, where they were cleaned of adherent fat and connective tissue. Rings of 4–5 mm in length were subsequently cut and opened from randomly selected areas of the vena cava and fixed by small pins with the endothelial surface up in 24-well culture dishes. In some experiments, vena caval segments from control rats and 25 mM D-glucose-injected rats were incubated with 0.04 U/ml insulin for 30 min. NO release into K-H solution warmed at 37°C was measured according to the method of Guo et al. (16) by use of an internally shielded polarographic NO electrode connected to a NO meter (Iso-NO Mark II, World Precision Instruments, Sarasota, FL). Calibration of the NO electrode was performed daily before each experimental protocol (17).

Determination of glucose concentrations in the blood and in the peritoneal fluid. Glucose concentrations in blood samples and in the peritoneal fluid samples were analyzed using an Accu-check Advantage blood glucose monitor (model no. 768,
Roche Diagnostic, Boehringer Mannheim, Indianapolis, IN). Samples were analyzed by applying a drop of blood or peritoneal fluid to a control strip inserted into the monitor. Quality control checks were made periodically using a test solution supplied by the manufacturer. Peritoneal fluid was collected immediately before intravital microscopy experiments by means of a sterile capillary pipette.

**Determination of plasma insulin concentrations.** Circulating blood concentrations of insulin were determined in control rats and rats injected with 25 mM D-glucose at 4 h postinjection. Blood samples were withdrawn from pentobarbital-anesthetized rats via tail vein puncture. Blood samples were anticoagulated with heparin and centrifuged at 3,000 g for 10 min to collect the plasma fraction. Insulin plasma concentrations were determined by an ELISA kit obtained from Calbiochem (Chicago, IL).

**Data Analysis**

All data are presented as means ± SE. Data were compared by analysis of variance (ANOVA) using post hoc analysis with Fisher’s corrected t-test. All data on leukocyte rolling and adherence and arterial blood pressure and shear rates were analyzed by ANOVA incorporating repeated measurements. Probabilities of ≤0.05 were considered statistically significant.

**RESULTS**

**Intravital Microscopy**

**Effects of increasing concentrations of D-glucose on leukocyte-endothelium interactions.** Single intraperitoneal injection of 6, 12.5, or 25 mmol/l glucose to rats did not result in any overt systemic hemodynamic effect, as confirmed by the absence of changes in mean arterial blood pressure in all experimental groups of rats. Mean arterial blood pressure values ranged from 137 ± 12 to 142 ± 17 mmHg [not significant (NS)]. Moreover, we examined mesenteric venules ranging from 26 ± 2 to 38 ± 3 μm in diameter (mean ± SE), and there was no difference in venular diameter among any of the groups studied. Shear rates in mesenteric venules were within the physiological range, with values ranging from 496 ± 58 to 739 ± 84 s⁻¹. This clearly indicates that a single exposure of the rat mesentery to 6, 12.5, and 25 mmol/l D-glucose does not change systemic hemodynamic or rheological factors over the 12-h observation time used in this study.

After single intraperitoneal injection of 25 mmol/l D-glucose, glucose levels in the peritoneal fluid increased to 160 ± 12 and 150 ± 8 mg/dl at 2 and 4 h, respectively. Subsequently, peritoneal fluid glucose levels declined 12 h postinjection (Fig. 1, left). Despite this intraperitoneal hyperglycemia, glucose levels in the blood of rats injected with 25 mmol/l D-glucose remained within the normal physiological range over the entire 12-h observation time with the highest value of 119 ± 4 mg/dl being recorded 4 h postinjection (Fig. 1, right). Because no significant changes in systemic blood glucose levels occurred, increased release of endogenous insulin was not a factor in this model of local hyperglycemia. In this regard, plasma insulin concentrations were found to be not significantly elevated 4 h after glucose loading (2.2 ± 0.4 vs. 1.8 ± 0.3 ng/ml insulin, in six 0.9% NaCl-injected rats vs. six 25 mM D-glucose-injected rats; NS).

![Fig. 1. Levels of glucose in peritoneal fluid (left) and in blood (right) 2, 4, and 12 h after single intraperitoneal (ip) injection with 25 mmol/l D-glucose. NS, not significant. All values are means ± SE; n = 6 rats in each group.](http://ajpendo.physiology.org/)}
A 12-h exposure of the rat mesentery to D-glucose at concentrations as low as 12.5 mmol/l induced a concentration-dependent increase in leukocyte rolling in post-capillary venules of the rat mesenteric microvasculature (Fig. 2, top). This phenomenon exhibited a more clear-cut pattern when 25 mmol/l D-glucose was injected in the rat peritoneal cavity, thus suggesting that the effect of D-glucose on leukocyte-endothelial cell interaction in vivo is concentration dependent.

Similarly, a concentration response to D-glucose was observed in the case of leukocyte adherence (Fig. 2, bottom). The number of leukocytes adhering to the venular endothelium was increased fivefold ($P < 0.01$) and sevenfold ($P < 0.01$) after intraperitoneal injection of 12.5 and 25 mmol/l D-glucose, respectively. Moreover, the number of transmigrated leukocytes was maximally increased by 25 mmol/l D-glucose from 1.8 ± 0.4 to 6 ± 0.5 cells/100 × 10 μm area (Fig. 3; $P < 0.01$), with most of the white cells being found in the perivascular area. Thus the biological signal resulting from a 12-h exposure to D-glucose is not a transient one.

None of these effects of D-glucose could be attributed to changes in ambient osmolarity, as demonstrated by the fact that intraperitoneal administration of 25 mmol/l L-glucose did not increase leukocyte rolling, adherence, and transmigration in rat mesenteric venules (Figs. 2 and 3).

In an additional set of experiments, we investigated the time course of the microvascular inflammatory response evoked by D-glucose in the rat mesenteric microcirculation. Analysis of leukocyte-endothelium interaction 2, 4, and 12 h after injection with 25 mmol/l D-glucose revealed a distinct time course for upregulation of leukocyte-endothelium interaction (Fig. 4). The resulting inflammatory response was characterized by a lag time of 2 h, with a significant increase in leukocyte rolling and leukocyte adherence beginning at 4 h postinjection (Fig. 4, top and bottom). Thus increases in ambient glucose lasting as long as 4 h initiate a microvascular inflammatory response that is concentration dependent, with concentrations as low as 12.5 mmol/l causing a significant yet submaximal effect.

We also studied the response to a single intraperitoneal injection of 25 mM D-glucose. In rat mesenteric venules, glucose-induced leukocyte-endothelium interactions started to decline 24 h postinjection and were completely recovered at 48 h postinjection. Thus only 22 ± 7 leukocytes/min were rolling and 3.5 ± 0.4 leukocytes/100 μm adhered in rat mesenteric venules 48 h postinjection. These values are not statistically different from values observed in control rats injected with saline.

Reversal of glucose-induced leukocyte-endothelium interaction by insulin. Because of the well known physiological role of insulin in regulating systemic and local glucose metabolism, we sought to investigate the effect of insulin on glucose-induced leukocyte-endothelium interactions in vivo. Local application of 0.05 U/min insulin onto the mesentery for 90 min markedly attenuated leukocyte rolling and leukocyte adherence induced by a 12-h exposure of the rat mesentery to intraperitoneal injection of 25 mmol/l D-glucose (Fig. 5, top and bottom). In particular, leukocyte rolling and leukocyte adherence were attenuated 55% ($P < 0.01$) and 45% ($P < 0.05$), respectively. In addition, insulin
inhibited D-glucose-induced transmigration of leukocytes across mesenteric venules from 6.7 ± 0.1.5 to 2.4 ± 0.7 cells/100 × 10-μm area (P < 0.01; n = 6). These values are significantly lower than those observed with glucose alone, indicating that insulin significantly and effectively prevented glucose-induced rolling and adherence.

Immunohistochemistry

Expression of the endothelial cell adhesion molecule P-selectin is illustrated in Fig. 6. Localization of P-selectin was accomplished using a modified avidin-biotin-immunoperoxidase technique. The percentage of venules staining positively for P-selectin in ileal sections from control rats receiving only K-H buffer or 25 mmol/l L-glucose was consistently low (i.e., ~15%; Fig. 6). However, exposure to 25 mmol/l D-glucose resulted in a time-dependent, increased expression of P-selectin as quantified by the percentage of venules staining positive for P-selectin from two- to threefold above control (P < 0.05 and P < 0.01 at 4 and 12 h, respectively). This represents a significant increase in the surface expression of P-selectin under these conditions. This increase in expression of P-selectin on ileal venules was significantly attenuated by application of 0.05 U/min of insulin for 90 min (Fig. 6). Thus glucose-induced P-selectin expression on the endothelial cell surface of the rat mesenteric microvasculature can be suppressed by exogenous insulin. These data are consistent with our functional data on leukocyte rolling, adherence, and transmigration.

Effect of Glucose on NO Release from Isolated Rat Vena Caval Segments

We detected a basal level of NO release averaging 12 ± 1.2 nmol/mg of tissue in inferior vena caval segments isolated from control rats injected with saline (Fig. 7). In contrast, release of NO from the inferior vena caval endothelium of rats given a single intraperitoneal injection of 25 mM D-glucose was reduced by 45% (P < 0.01; Fig. 7). In addition, incubation of vena caval segments with 0.04 U/ml for 30 min resulted in a 2.5-fold increase in NO release (P < 0.001 vs. control vena caval tissue from glucose injected animals; Fig. 7). Therefore, exposure of the peritoneal cavity to 25 mM D-glucose induced a marked degree of endothelial dysfunction in the vascular endothelium of the inferior vena cava characterized by a reduction in NO release, and this endothelial dysfunction is attenuated by insulin.

![Fig. 5. Effects of insulin on leukocyte-endothelium interaction induced by D-glucose. Insulin was superfused on the exposed mesentery at a concentration of 0.05 U/min for 90 min. The effect of insulin on leukocyte rolling (top) and leukocyte adherence (bottom) was studied in rat mesenteries exposed to a single ip administration of 25 mmol/l D-glucose. Observations were made 12 h after glucose injection. All values are means ± SE. Nos. in parentheses are nos. of rats in each group. Insulin markedly attenuated glucose-induced leukocyte-endothelium interaction.](http://ajpendo.physiology.org/)}
DISCUSSION

The present study demonstrates that acute exposure of the vascular endothelium to elevated ambient glucose upregulates leukocyte-endothelium interaction in the rat mesenteric microcirculation in vivo, via a P-selectin-dependent mechanism, and depresses release of NO in the inferior vena cava. In addition, we provide evidence that local application of insulin attenuates leukocyte-endothelial cell interactions induced by concentrations of glucose comparable to those found in the blood of diabetic patients.

Hyperglycemia is considered to be a major contributor to diabetic angiopathy (7). In vitro and in vivo studies have demonstrated that acute exposure of the vascular endothelium to elevated glucose levels results in a reduced release of NO (21, 47) and increased expression of endothelial cell adhesion molecules (30, 35). Circulating levels of cell adhesion molecules have been found to be significantly elevated also in the plasma of diabetic patients (27). In addition, several experimental animal models of diabetes have clearly demonstrated that exposure of the vascular wall to increased blood glucose levels rapidly results in profound alterations of the homeostasis of the entire vessel wall. In this regard, increased generation of oxygen-derived free radicals has been reported throughout the carotid artery of diabetic rabbits (25). Similarly, daily intraperitoneal injections of glucose to the rats for 4–5 wk induce functional and morphological changes that are similar to those observed in diabetic animals (4). Despite the numerous reports of endothelial dysfunction in diabetes, the time course as well as the concentration response of glucose-induced endothelial dysfunction in the pathophysiology of the diabetic microangiopathy remain unclear.

Reduced release of NO is a common pathophysiological event of acute (43) and chronic (19) inflammatory conditions of the vasculature. Because of the anti-
Glucose-Induced Leukocyte-Endothelium Interactions

Inflammatory role of physiological concentrations of NO, it is likely that loss of endothelium-derived NO during hyperglycemia initiates an inflammatory response via increased synthesis and cell surface expression of adhesion molecules (24). In this regard, NO has been shown to downregulate surface expression of endothelial cell adhesion molecules via inhibition of NF-κB activity (10). Moreover, because NO quenches oxygen radicals (36), reduced synthesis or release of NO leads to the existence of enhanced superoxide anions with greater ability to upregulate endothelial cell surface expression of cell adhesion molecules such as P-selectin (2).

Several investigators have demonstrated that acute hyperglycemia depletes arteriolar NO formation in the intestinal (5) and cerebral (28) microvasculature of rats as well as in skeletal muscle arterioles (21). Acute hyperglycemia impairs endothelium-dependent vasodilation also in healthy humans in vivo (47), with endothelial dysfunction occurring 6 h after exposure of the brachial artery to 300 mg/dl of d-glucose.

During diabetes, impaired endothelial function has been associated with either reduced NO bioavailability or decreased sensitivity of the vascular cells (e.g., smooth muscle layer) to NO (11). Thus several mechanisms of endothelial dysfunction have been reported, including impaired signal transduction or substrate availability, impaired release of NO, increased degradation of NO, enhanced release of endothelium-derived constricting factors, and decreased sensitivity of vascular smooth muscle cells to NO (11). In this regard, this is the first study to demonstrate that exposure of the vascular endothelium to elevated ambient glucose for as short a duration as 4 h results in a significant and acute loss of NO, as confirmed by direct measurement of NO release in inferior vena cava of glucose-injected rats.

This key finding correlates with our observation of increased leukocyte-endothelium interaction in the rat mesenteric microvasculature beginning 4 h after exposure of the microcirculation to elevated concentrations of glucose as low as 225 mg/dl. Therefore, a direct correlation can be established between loss of endothelial NO and increased leukocyte-endothelium interactions in the diabetic microcirculation.

Under physiological conditions, NO exerts distinct anti-inflammatory effects by preserving endothelial cell integrity (24) and preventing both cell surface expression (32) and de novo synthesis of adhesion molecules (2, 10). In the absence of this immunomodulatory effect of NO, circulating leukocytes become tethered to the vascular endothelium, where they become activated by a process involving cell-to-cell signaling. In vitro studies have clearly shown that elevated ambient glucose increases the adhesiveness of isolated white cells to cultured endothelial cells (30, 34). This phenomenon is associated with upregulation of ICAM-1 (3) and PECAM-1 (34) glycoproteins. In addition, high levels of circulating adhesion molecules were found in the blood of healthy volunteers after intravenous infusion of glucose, as well in type 2 diabetic patients (27).

Among the adhesion molecules, P-selectin plays a strategic role in the inflammatory process as it regulates leukocyte rolling, the first step of leukocyte-endothelium interactions. Leukocyte rolling is a prerequisite for firm adherence, because integrin-mediated adherence is relatively ineffective at physiological shear rates (22). In this regard, several investigators have demonstrated that inhibition of the rolling phase of leukocytes plays a key role in moderating the inflammatory response (9, 44).

Contact of circulating leukocytes with the vascular endothelium promotes a cascade of events that leads to leukocyte activation. Once activated, leukocytes are able to release oxygen-derived free radicals, proteolytic enzymes, and cytokines (45). Superoxide radicals released from leukocytes have been shown to inactivate NO (36), induce vasoconstriction (31), and disrupt cellular membranes through lipid peroxidation (45). All these processes lead to further leukocyte activation and aggravate vascular endothelial dysfunction. In particular, leukocyte stasis, as well as infiltration of circulating leukocytes in the perivascular area, can have detrimental effects in diabetes, as leukocytes contribute to vasoconstriction and endothelial cell injury in diabetic microangiopathy (26).

In our experimental model of local hyperglycemia, local application of insulin was able to significantly attenuate leukocyte-endothelium interactions induced by glucose. In this regard, it has been demonstrated that insulin stimulates the release of NO in endothelial cells (41) via two different signaling pathways that involve both phosphatidylinositol 3-kinase and protein kinase B (48). Therefore, it is conceivable that insulin inhibited leukocyte rolling and leukocyte adherence via increased release of NO from the vascular endothelium of the rat mesenteric microvasculature. However, the nature of this immunomodulatory action of insulin during hyperglycemia and of how it relates to the NO biosynthetic pathway needs further investigation.

Taken together, these data clearly demonstrate that upregulation of leukocyte-endothelium interactions associated with loss of endothelial NO release occurs very early after exposure of the vascular endothelium to elevated glucose levels. These data also help to further explain previous observations showing a heightened inflammatory response in the mesenteric microcirculation of streptozotocin-induced diabetic rats (33) and nondiabetic rats given a continuous intravenous infusion of glucose (38). More recently, Schaffer et al. (39) showed that the inflammatory response induced by elevated blood glucose levels in the rat mesentry in vivo can be partially blocked via inhibition of both protein kinase C (PKC) and p38 mitogen-activated protein (MAP) kinase. However, the mechanism by which inhibition of PKC and p38 MAP kinase pathways suppresses leukocyte-endothelium interactions remains unclear. One possibility is that PKC activity in endothelial cells is physiologically regulated by basal release of NO. In this regard, we have previously demonstrated that activation of PKC by atherogenic phospholipids rapidly induces P-selectin expression in
both platelets and endothelial cells, and that NO-generating agents are able to inhibit PKC-induced upregulation of P-selectin (32). The present study demonstrates that upregulation of P-selectin in the rat mesenteric microvasculature, as well as reduced release of NO from the rat aortic endothelium, occurs in response to elevated ambient glucose. Therefore, these data may help explain a key mechanism by which glucose-induced activation of protein kinase pathways in endothelial cells initiates inflammatory events within the microcirculation.

In conclusion, this is the first in vivo study to demonstrate that an acute increase in ambient glucose causes a rapid inflammatory response in the microcirculation. This rapid response appears to be triggered via upregulation of P-selectin on the endothelial cell surface, probably due to reduced endothelium-derived NO. This phenomenon may represent an important early mechanism of the diabetic microangiopathy.

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