Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection

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Obesity, diabetes, and related manifestations are associated with an enhanced, but poorly understood, risk for mucosal infection and systemic inflammation. Here, we show in mouse models of obesity and diabetes that hyperglycemia drives intestinal barrier permeability, through GLUT2-dependent transcriptional reprogramming of intestinal epithelial cells and alteration of tight and adherence junction integrity. Consequently, hyperglycemia-mediated barrier disruption leads to systemic influx of microbial products and enhanced dissemination of enteric infection. Treatment of hyperglycemia, intestinal epithelial–specific GLUT2 deletion, or inhibition of glucose metabolism restores barrier function and bacterial containment. In humans, systemic influx of intestinal microbiome products correlates with individualized glycemic control, indicated by glycated hemoglobin levels. Together, our results mechanistically link hyperglycemia and intestinal barrier function with systemic infectious and inflammatory consequences of obesity and diabetes.

The obesity pandemic has reached alarming magnitudes, affecting more than 2 billion people worldwide and accounting for more than 3 million deaths per year (1). A poorly understood feature of the “metabolic syndrome” is its association with dysfunctions of the intestinal barrier, leading to enhanced permeability and translocation of microbial molecules to the intestinal lamina propria and systemic circulation (2). This influx of immune-stimulatory microbial ligands into the vasculature, in turn, has been suggested to underlie the chronic inflammatory processes that are frequently observed in obesity and its complications (3), while entry of pathogens and pathobionts through an impaired barrier leads to an enhanced risk of infection in obese and diabetic individuals (4, 5), particularly at mucosal sites (6). However, the mechanistic basis for barrier dysfunction accompanying the metabolic syndrome remains poorly understood. Beyond metabolic disease, enhanced intestinal permeability has also been linked with systemic inflammation in a variety of conditions, including cancer (7), neurodegeneration (8), and aging (9). Thus, there is an urgent scientific need to better define the molecular and cellular orchestrators and disruptors of intestinal barrier function, to devise strategies to counteract the detrimental systemic consequences of gut barrier alterations.

Obesity is associated with, but not required for, intestinal barrier dysfunction

We began our investigation of the drivers of gastrointestinal barrier dysfunction in obesity by hypothesizing that the adipokine leptin, a major orchestrator of mammalian satiety, may act as an obesity-associated regulator of barrier integrity. Leptin deficiency and resistance to leptin signaling are strongly associated with morbid obesity in mice and humans, and both leptin deficiency and resistance were previously suggested to contribute to intestinal barrier dysfunction and susceptibility to enteric infection (10–13). We used a mouse model featuring genetic deletion of leptin receptor (LepR), leading to hyperphagia and morbid obesity (db/db, fig. S1A). Indeed, we detected elevated amounts of microbial pattern recognition receptor (PRR) ligands at multiple systemic sites in leptin-unresponsive db/db mice (Fig. 1, A to C), indicative of enhanced influx of gut commensal-derived products. A similar phenomenon was observed in leptin-deficient mice (db/db, fig. S1, B and C). To gain insight into the molecular signatures accompanying barrier dysfunction under aberrant leptin signaling, we performed RNA sequencing of colonic tissue, obtained from db/db mice and their wild-type (WT) littermates under steady-state conditions. Leptin unresponsiveness was associated with global alterations of transcription (fig. S1D), with several hundred genes featuring differential expression between both groups (fig. S1E). Among the genes whose expression was most strongly abrogated in obese mice were members of the tight and adherence junction structures (fig. S1F), protein complexes that inhibit paracellular flux of intestinal molecules into the lamina propria (14). Consequently, tight junction integrity was compromised in db/db mice (Fig. 1, D and E), leading to enhanced influx of luminal molecules and electrical current measured across the epithelial layer (Fig. 1, F and G).

To determine the consequences of barrier dysfunction in leptin-resistant mice, we used the murine Citrobacter rodentium model simulating human enteropathogenic Escherichia coli infection (15). A bioluminescent variant of C. rodentium allowed us to noninvasively track infection in vivo (16). In WT mice, C. rodentium caused a self-limiting, mainly gut-contained infection (Fig. 1, H to L). In contrast, db/db mice did not clear the pathogen from their intestine (Fig. 1, H and I), in line with previous reports (12). Notably, db/db mice also showed a significantly enhanced bacterial attachment to the intestinal wall (fig. S1, G and H) and featured C. rodentium colonization at systemic sites (Fig. 1, J to L, and fig. S1I). Similar susceptibility to C. rodentium was noted for leptin-deficient ob/ob mice (fig. S1, J to N).

To understand which cell type was responsible for LepR-mediated protection from enteric infection, we generated bone marrow chimeras, in which WT and db/db mice were used as either recipients or donors of bone marrow transplanted into lethally irradiated mice. Exacerbated infection and systemic spread of C. rodentium was observed whenever the bone marrow recipient was LepR-deficient, regardless of the source of bone marrow (Fig. 1, M and N, and fig. S1O), indicating that the nonhematopoietic compartment mediated resistance against infection. LepR expression on nonhematopoietic cells has been reported in multiple tissues, including the gut, liver, and most prominently the nervous system (17). Mice lacking LepR in intestinal epithelial cells (Villin-Cre:LepRfl/fl) or hepatocytes (Albumin-Cre:LepRfl/fl) did not show any signs of enhanced susceptibility to C. rodentium infection (fig. S2, A to F), whereas mice with LepR deficiency specifically in the nervous system (Nestin-Cre:LepRfl/fl) featured an exacerbated (fig. S2, G to I), yet highly variable (fig. S2, J to O), bacterial growth. To further exploit the possibility of neuronal leptin signaling driving barrier dysfunction and risk of infection, we generated mice with a specific
deletion of LepR in the paraventricular hypothalamus (Sim1-Cre:LepR<sup>fl/fl</sup>), in the ventromedial hypothalamus (SF1-Cre:LepR<sup>fl/fl</sup>), in cholinergic neurons (ChAT-Cre:LepR<sup>fl/fl</sup>), and in the arcuate nucleus of the hypothalamus (POMC-Cre:LepR<sup>fl/fl</sup> and AgRP-Cre:LepR<sup>fl/fl</sup>) and infected them with <i>C. rodentium</i>. However, none of these mice showed enhanced susceptibility to pathogenic invasion when compared to littermate controls (fig. S3, A to O). Collectively, these results suggested that leptin deficiency per se might not provide a sufficient explanation to barrier dysfunction and enhanced risk of enteric infection.

A feature common to all leptin- and LepR-deficient mice exhibiting an impaired barrier function and enhanced <i>C. rodentium</i> dissemination in our studies (<i>db/db</i>, ob/ob and Nestin-Cre:LepR<sup>fl/fl</sup>) was their tendency to develop obesity. We therefore hypothesized that an obesity-related factor distinct from leptin signaling may predispose these mice to impaired barrier function and exacerbated intestinal infection. Thus, to complement the above genetic models of obesity, we fed WT mice a high-fat diet (HFD) to induce weight gain (fig. S4A). Similarly to obese leptin- and LepR-deficient mice, HFD-fed obese mice showed elevated steady-state systemic PRR ligand influx (Fig. 2A), as well as exacerbated <i>C. rodentium</i> infection and systemic dissemination (Fig. 2, B to E, and fig. S4B). To further test whether obesity is the major driver for barrier dysfunction and impaired <i>C. rodentium</i> containment in LepR-deficient mice, we performed paired-feeding experiments, in which the food access for <i>db/db</i> mice was restricted to the amount consumed by their WT littermates, thereby equalizing body weight between both groups (Fig. 2F). Surprisingly, even after weight reduction to control levels, lean <i>db/db</i> mice were still unable to cope with <i>C. rodentium</i> infection (Fig. 2, G and H), ruling out that obesity per se was directly driving barrier dysfunction and risk for enteric infection in these mice. The lack of a direct causal relationship between obesity and barrier dysfunction was further supported by experiments using a chemical inhibitor of leptin signaling (18), which rendered WT mice susceptible to exacerbated infection and systemic bacterial spread even before the onset of marked obesity (Fig. 2, I to L, and fig. S4, C to F). Together, these data indicated that neither leptin signaling nor obesity per se sufficiently explain the severity of barrier dysfunction and systemic enteric infection in mice with the metabolic syndrome.

In search of a unifying explanation for the above results in multiple mouse models of genetic and acquired obesity and leptin deficiency, we investigated other common features of the metabolic syndrome that could potentially contribute to barrier dysfunction. One such manifestation...
of the metabolic syndrome, typically accompanying obesity and potentially contributing to barrier dysfunction, is glucose intolerance and resultant hyperglycemia. Notably, all mice featuring marked susceptibility to C. rodentium infection, including obese db/db, pair-fed lean db/db mice, Nestin-Cre:LepR<sup>fl/fl</sup> mice, mice fed a HFD, and mice treated with leptin antagonist, showed elevated blood glucose concentrations (Fig. 2, M to O, and fig. S4, G and H). In contrast, all mouse groups and models that did not develop enhanced C. rodentium susceptibility (Villin-Cre:LepR<sup>fl/fl</sup>, Albumin-Cre:LepR<sup>fl/fl</sup>, Sim1-Cre:LepR<sup>fl/fl</sup>, SPT-Cre:LepR<sup>fl/fl</sup>, ChAT-Cre:LepR<sup>fl/fl</sup>, POMC-Cre:LepR<sup>fl/fl</sup>, and AgRP-Cre:LepR<sup>fl/fl</sup>) as well as those Nestin-Cre:LepR<sup>fl/fl</sup> mice that did not feature a tendency for severe infection (fig. S4, I and J). Together, these results suggested that hyperglycemia, rather than obesity or alterations in leptin signaling, may predispose to barrier dysfunction leading to enhanced enteric infection in the setup of the metabolic syndrome in mice.

**Hyperglycemia drives intestinal barrier disruption**

To test whether elevated glucose concentrations were causally involved in host defense against intestinal infection, we induced hyperglycemia in the absence of obesity in a mouse model of type 1 diabetes mellitus through administration of streptozotocin (STZ) (19), fig. S5A). Indeed, STZ-treated mice developed severe C. rodentium infection and systemic translocation, accompanied by enhanced bacterial growth, epithelial adherence, and systemic spread (Fig. 3, A to E). STZ treatment also resulted in dysfunction of intestinal epithelial adherence junctions under steady-state conditions (Fig. 3, F and G), coupled with systemic dissemination of microbial products (fig. S5, B and C), and enhanced transepithelial flux (Fig. 3, H and I).

**Oral antibiotic treatment prevented the detection of bacterial products at systemic sites in STZ-treated mice (Fig. 3, J to L), demonstrating that the intestinal microbiota was the probable source of disseminated microbial molecules. Indeed, 16S ribosomal DNA (rDNA) sequencing revealed a taxonomic change in the configuration of the intestinal microbiota of hyperglycemic mice, which was corrected by insulin treatment and resultant normalization of serum glucose concentrations (fig. S6, A to D). However, these compositional microbial changes did not seem to play a critical role in glucose-mediated barrier dysfunction, as microbiota transfer from STZ-treated

![Fig. 2. Obesity does not suffice to explain susceptibility to enteric infection.](http://science.sciencemag.org/)

(A) PRR stimulation by splenic extracts from mice fed a high-fat diet (HFD). (B to E) Abdominal luminescence (B) and CFUs recovered from colonic tissue (C), spleens (D), and livers (E) of HFD-fed mice infected with luminescent C. rodentium. (F to H) Body weight (F), C. rodentium luminescence (G), and C. rodentium-induced mortality (H) in paired-fed db/db mice and controls. (I to L) Total abdominal luminescence signals (I) and live CFUs recovered from colonic tissue (J), mesenteric lymph nodes, (K) and livers (L) from leptin antagonist (LeptAnt)-treated mice infected with bioluminescent C. rodentium. (M to O) Blood glucose concentrations in paired-fed db/db mice (M), HFD-fed mice (N), and LeptAnt-treated mice (O). All data represent at least two independent experiments. Means ± SEM are plotted. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001 by ANOVA (F and M) or Mann-Whitney U test (all other panels).
donors and controls to normoglycemic germ-free mice neither induced dissemination of bacterial products to systemic sites (fig. S6E) nor increased susceptibility to C. rodentium infection (fig. S6, F to J). These data indicate that although the commensal microbiota serves as the reservoir of microbial molecules that translocate to the systemic circulation upon disruption of the intestinal barrier, compositional microbiota alterations arising under hyperglycemic conditions do not directly affect barrier integrity.

To corroborate the specificity of hyperglycemia as a driver of susceptibility to intestinal infection, we used hyperglycemic Akita mice (fig. S7A), an STZ-independent model of type 1 diabetes mellitus that harbors a spontaneous mutation in the gene encoding insulin 2 (20). As in STZ-treated mice, we observed in this model elevated C. rodentium growth and pathogenic translocation to systemic tissues (Fig. 3, M and N, and fig. S7, B and C). To further validate the specific impact of hyperglycemia as a driver of the barrier dysfunction phenotype, we administered 0.25 U per day of insulin to STZ-treated mice via hyperosmotic pumps for 4 weeks, which restored normoglycemic levels (fig. S7D). Treatment with insulin also prevented the loss of adherence junction integrity (Fig. 4A and fig. S7E), systemic dissemination of microbial products (Fig. 4B), and enhanced C. rodentium growth and pathogenic translocation (Fig. 4, C and D). Together, these experiments establish hyperglycemia as a direct and specific cause for intestinal barrier dysfunction and susceptibility to enteric infection.

**Hyperglycemia reprograms intestinal epithelial cells**

To determine whether glucose acted directly on intestinal epithelial cells to affect barrier function, we used an in vitro system of cultured intestinal epithelial (Caco-2) cells exposed to different concentrations of glucose in the culture medium. We assessed tight junction integrity through automated high-throughput analysis of ZO-1 staining patterns. Indeed, glucose induced barrier alterations in a dose- and time-dependent manner, manifesting visually as increased tortuosity and altered appearance of cell-cell junctions (Fig. 4, E to H). To investigate the mechanisms by which elevated blood glucose concentrations compromise intestinal epithelial cell function in vivo, we performed RNA sequencing of purified intestinal epithelial cells from STZ-treated mice and controls. Global reprogramming of the epithelial transcriptome was detected in hyperglycemic mice (Fig. 4I), in which more than 1000 genes were differentially expressed compared to vehicle-treated controls (Fig. 4J). These genes were predominantly involved in metabolic pathways, and specifically in N-glycan biosynthesis and pentose-glucuronate interconversion (Fig. 4K), two intracellular functions critically involved in the maintenance of epithelial barrier function (21–29). For example, hyperglycemia affected the entire pathway of protein N-glycosylation by provoking marked downregulation of central genes (Fig. 4L and fig. S8). In contrast, epithelial proliferation or cell death were not affected by STZ treatment (fig. S9, A to D).

In addition to the above epithelial changes, hyperglycemia modestly affected the intestinal epithelial transcriptome. We observed evidence of glucose-induced reprogramming of the epithelial transcriptome as early as 3 days after oral gavage. (J) Detection of 16S rDNA in livers of STZ- and Abx-treated mice. (K and L) PRR stimulation by sera (K) and hepatic extracts (L) from STZ-treated mice and controls, with or without antibiotic (Abx) treatment. (M and N) Abdominal luminescence (M) and hepatic CFUs (N) from C. rodentium–infected Akita mice. All data represent at least two independent experiments. Means ± SEM are plotted. *P < 0.05, ***P < 0.001, ****P < 0.0001 by ANOVA (J) or Mann-Whitney U test (all other panels).
and splenic immune system, specifically by causing an increased representation of myeloid cells (Fig. S10, A to J), in line with previous reports (30). However, STZ treatment did not provoke an overt inflammatory state in the intestine (Fig. S11, A to E). In particular, cytokines involved in interleukin-22 (IL-22)–mediated barrier function and host defense, which has been implicated in the susceptibility of obese mice to infection (19), were unaltered, as was the epithelial transcriptional response to IL-22 (fig. S11F). Indeed, hyperglycemia involves glucose metabolism and GLUT2 expression in epithelial cells from hyperglycemic mice (Fig. 4A to E). In contrast to this marked susceptibility of STZ-treated mice to oral Salmonella Typhimurium infection, susceptibility of these mice to systemic infection was only apparent in the liver (Fig. S12, F to H). Notably, systemic infection with Salmonella caused enhanced intestinal colonization in STZ-treated mice, potentially indicative of retrograde spread of bacteria across a compromised barrier (Fig. S12, I and J).

**Epithelial reprogramming by hyperglycemia involves glucose metabolism and GLUT2**

We next assessed whether epithelial glucose metabolism was involved in the transcriptional reprogramming of STZ-treated mice. Isolated intestinal epithelial cells from hyperglycemic mice featured elevated amounts of metabolites along the glycolytic cascade (Fig. S13A). Inhibition of glucose metabolism via 2-deoxyglucose (2-DG) rescued glucose-induced barrier aberrations in vitro in a dose-dependent manner (Fig. 5, A to C). In addition, 2-DG administration blocked transcriptional reprogramming in STZ-treated mice (Fig. 5D and fig. S13B), including the N-glycan pathway (fig. S13C); prevented the systemic dissemination of microbial products (Fig. 5, E and F); and restored host defense against C. rodentium infection (Fig. 5G and fig. S13, D to F). Bacterial growth in the intestinal lumen was unaffected by 2-DG treatment (fig. S13G). To test whether 2-DG could be used to counteract hyperglycemia-mediated loss of barrier integrity beyond the STZ model, we administered 2-DG to C. rodentium–infected db/db mice and assessed its impact on systemic dissemination of the pathogen. Notably, the detectable pathogen load in the mesenteric lymph nodes, spleens, and livers of 2-DG–treated db/db mice was strongly reduced under 2-DG treatment (Fig. 5H and fig. S13, I to K). Together, these data suggest that glucose-mediated reprogramming of epithelial cell metabolic function leads to transcriptional alterations, abrogation of the intestinal barrier, and impaired host defense against enteric infection.

Glucose transport between the intestinal epithelium and circulation is mediated by the bidirectional glucose transporter GLUT2 (32). To determine the role of this transporter in hyperglycemia-mediated epithelial reprogramming, we next used mice selectively lacking GLUT2 in intestinal epithelial cells (GLUT2IEC) and induced hyperglycemia in these mice by STZ administration. Indeed, GLUT2IEC mice were resistant to STZ-induced transcriptional reprogramming and retained epithelial transcriptomes similar to those of controls (fig. S14, A and B). Similarity matrix of the epithelial transcriptomes of STZ-treated mice, with or without 2-DG administration (E and F) PRR stimulation by hepatic extracts (E) and sera (F) from STZ-treated mice, with or without 2-DG administration. (G and H) Splenic CFUs from C. rodentium–infected and 2-DG–treated STZ (G) and db/db mice (H). (I to K) Colonic ZO-1 (I) and E-cadherin intensity (J) and PRR stimulation by hepatic extracts (K) from STZ-treated GLUT2IEC mice and controls. (L) CFUs recovered from spleens of STZ-treated GLUT2IEC mice and controls infected with C. rodentium. All data represent at least two independent experiments. Means ± SEM are plotted. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001 by ANOVA.

Blood glucose concentrations are associated with microbial product influx in humans

Finally, we sought to determine whether glycemic levels similarly correlate with intestinal barrier function in humans. To this end, we recruited 27 healthy individuals (fig. S15, A and B) and performed measurements of multiple serum parameters and microbial products in the circulation. Of all variables measured, hemoglobin A1c (HbA1c), indicative of an individual’s 3-month average plasma glucose concentration, showed the strongest correlation with serum levels of PRR ligands (Fig. 6, A to C, and fig. S15, C to E). In contrast, high body mass index and other parameters and microbial products in the circulation correlated with or potentially even drive intestinal barrier dysfunction in humans.

Discussion

Serum glucose is among the most strictly controlled physiological variables of organismal homeostasis. Chronically elevated glucose concentrations, as observed in diabetes mellitus, obesity, and associated metabolic disorders, such as nonalcoholic fatty liver disease, result from altered homeostatic set points of the tightly regulated normoglycemic levels (33). Long-standing hyperglycemia, in turn, leads to a myriad of potentially devastating biochemical and physiological consequences, such as the generation of advanced glycation end products, pancreatic glucose toxicity (34, 35), macrovascular and microvascular complications affecting virtually every organ (36), risk of infection (37), and enhanced mortality (38).

In this study, we have identified glucose as an orchestrator of intestinal barrier function. Hyperglycemia markedly interfered with homeostatic epithelial integrity, leading to abnormal influx of...
Hyperglycemia is associated with influx of microbial products in humans. (A and B) Correlation matrix (A) and average correlations with systemic PRR ligands (B) of the indicated parameters in the serum of 27 healthy volunteers. (C) Correlation of HbA1c with serum levels of TLR4 ligands.

Systemic PRR ligands (B) of the indicated parameters in the serum of 27 healthy volunteers. (C) Correlation of HbA1c with serum levels of TLR4 ligands.

**REFERENCES AND NOTES**


**Fig. 6. Hyperglycemia is associated with influx of microbial products in humans. (A and B) Correlation matrix (A) and average correlations with systemic PRR ligands (B) of the indicated parameters in the serum of 27 healthy volunteers. (C) Correlation of HbA1c with serum levels of TLR4 ligands.**
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Author contributions: C.A.T. conceived the study, supervised and mentored its participants, interpreted results, and wrote the manuscript. Competing interests: The authors declare that they have no competing interests.

Data and materials availability: All data and code to understand and assess the conclusions of this research are available in the main text, supplementary materials, and via the following repositories: European Nucleotide Archive (ENA) accession no. PRJEB24760. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

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SUPPLEMENTARY MATERIALS
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Data and materials availability: The authors declare that they have no competing interests.

All data and code to understand and assess the conclusions of this research are available in the main text, supplementary materials, and via the following repositories: European Nucleotide Archive (ENA) accession no. PRJEB24760. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

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Materials and Methods

Figs. 51 to 56

References (47–56)

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Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection


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Metabolic syndrome, leaky guts, and infection

Metabolic syndrome often accompanies obesity and hyperglycemia and is associated with a breakdown in the integrity of the intestinal barrier and increased risk of systemic infection. Thaiss et al. found that mice with systemic infection of a Salmonella analog, Citrobacter rodentium, also exhibited hyperglycemia. Deletion of the glucose transporter GLUT2 altered sensitivity to chemically induced epithelial permeability and protected mice from pathogen invasion. The authors also found a correlation in humans between glycated hemoglobin (an indicator of hyperglycemia) and serum levels of pathogen recognition receptor ligands.

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