Role of the Gut Microbiome in Obstructive Sleep Apnea–Induced Hypertension

David J. Durgan, Bhanu P. Ganesh, Julia L. Cope, Nadim J. Ajami, Sharon C. Phillips, Joseph F. Petrosino, Emily B. Hollister, Robert M. Bryan Jr

Abstract—Individuals suffering from obstructive sleep apnea (OSA) are at increased risk for systemic hypertension. The importance of a healthy gut microbiota, and detriment of a dysbiotic microbiota, on host physiology is becoming increasingly evident. We tested the hypothesis that gut dysbiosis contributes to hypertension observed with OSA. OSA was modeled in rats by inflating a tracheal balloon during the sleep cycle (10-s inflations, 60 per hour). On normal chow diet, OSA had no effect on blood pressure; however, in rats fed a high-fat diet, blood pressure increased 24 and 29 mm Hg after 7 and 14 days of OSA, respectively ($P<0.05$ each). Bacterial community characterization was performed on fecal pellets isolated before and after 14 days of OSA in chow and high-fat fed rats. High-fat diet and OSA led to significant alterations of the gut microbiota, including decreases in bacterial taxa known to produce the short chain fatty acid butyrate ($P<0.05$). Finally, transplant of dysbiotic cecal contents from hypertensive OSA rats on high-fat diet into OSA recipient rats on normal chow diet (shown to be normotensive) resulted in hypertension similar to that of the donor (increased 14 and 32 mm Hg after 7 and 14 days of OSA, respectively; $P<0.05$). These studies demonstrate a causal relationship between gut dysbiosis and hypertension, and suggest that manipulation of the microbiota may be a viable treatment for OSA-induced, and possibly other forms of, hypertension. **(*Hypertension*. 2016;67:469-474. DOI: 10.1161/HYPERTENSIONAHA.115.06672.)** • **Online Data Supplement**

Key Words: butyrates ■ dysbiosis ■ hypertension ■ microbiota ■ obstructive sleep apnea

Obstructive sleep apnea (OSA) is a prevalent disorder characterized by repeated collapse of the upper airway during sleep.[1,2] Individual apneic episodes lead to transient hypoxia, hypercapnia, and excessive negative intrathoracic pressures as the patient attempts to breathe against a closed airway.[2,3] In addition, sympathetic activity is increased with arousal when each apnea is resolved.[3] Estimates suggest that 5% to 25% of the adult Western population has clinically significant OSA.[1] Risk factors for OSA, including obesity and aging, are on the rise, suggesting that the burden of OSA will continue to increase in the coming years.[2]

OSA is a significant risk factor for numerous cardiovascular diseases and in many cases increases the disease severity and progression.[2,3] The prevalence of OSA in primary hypertension is ≈35%.[4] In patients with drug-resistant hypertension, the prevalence of OSA climbs to ≈65% to 80%.[5–7] Furthermore, treatment of OSA in this population is more successful at lowering blood pressure than multiple drugs, suggesting OSA plays an integral role in hypertension.[8]

Commensal bacteria cover every surface of our body exposed to the environment. These bacteria, termed microbiota, outnumber our own cells 10:1, with 70% of these residing in the gastrointestinal tract.[9] Under normal conditions, there is a mutualistic relationship between the host and gut microbiota. The host provides nutrition and a suitable living environment for the bacteria, whereas the microbiota aid in maintenance of immune response, act as a barrier from invasive pathogens, and contribute nutrients to the host.[10,11] This mutualistic relationship can be compromised by shifts in the composition of the microbiota, termed dysbiosis. Proposed triggers for these bacterial shifts include the overuse of selected antibiotics, infectious agents, and diet.[9] Dysbiosis in the gut has been linked to inflammatory disorders including inflammatory bowel disease, metabolic disorders including obesity and diabetes mellitus, neurological diseases including autism spectrum disorder, and atherosclerotic heart disease.[12,13] In this study, we tested the hypothesis that gut dysbiosis contributes to the hypertension observed in OSA.

Materials and Methods

Detailed Materials and Methods are available in the online-only Data Supplement.

Animal procedures were performed in accordance with the *Guide for the Care and Use of Laboratory Animals, 8th edition,* published by the National Institutes of Health, and they were approved by the Institutional Animal Care and Use Committee at Baylor College of

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From the Departments of Anesthesiology (D.J.D., S.C.P., R.M.B.), Pathology and Immunology (B.P.G., J.L.C., E.B.H.), Molecular Physiology and Biophysics (R.M.B.), The Alkek Center for Metagenomics and Microbiome Research, Department of Molecular Virology and Microbiology (N.J.A., J.F.P.), and Texas Children's Microbiome Center, Department of Pathology, Baylor College of Medicine, Houston (J.L.C., E.B.H.); and Department of Medicine, Texas Children's Hospital, Houston (J.L.C., E.B.H.).

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Correspondence to David J. Durgan, Department of Anesthesiology, Baylor College of Medicine, One Baylor Plaza, Room 434D, Houston, TX 77030. E-mail durgan@bcm.edu

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Medicine, Houston, TX. Long Evans rats were housed with a 12-hour light (6 AM–6 PM): 12-hour dark (6 PM–6 AM) cycle. At 8 to 9 weeks old, a sub set of rats were switched from normal chow to a high-fat diet (60% calories from fat) for the remainder of the study (5 weeks total).

Endotracheal Obstruction Device Implantation

Rats, 10 to 11 weeks old, were implanted with an endotracheal obstruction device as described previously.[14,15] Sham rats underwent identical surgical procedures and device implantation, but endotracheal obstruction devices were never inflated. Rats that underwent periods of apnea are referred to as OSA rats and the sham-controls are referred to as sham rats.

Experimental Alterations of the Gut Microbiota

The gut microbiota were altered by antibiotics or cecal contents transplantations. Details of each protocol are outlined in the online-only Data Supplement.

Noninvasive Blood Pressure Measurements

Tail-cuff plethysmography (Harvard Apparatus) was used to measure systolic blood pressure in unanesthetized rats between 8 AM and noon, before, and after 7 and 14 days of OSA or sham. A minimum of 5 consecutive readings, without movement artifact, were averaged for each measurement.

Gut Microbiota Analysis

Fecal samples were collected in sterile tubes before and after 14 days of OSA or sham and stored at −80°C. Detailed methods for identification and analysis of the gut microbiota makeup, using 16S rRNA sequences, are outlined in the online-only Data Supplement.

Statistics

Line and bar plot data are expressed as mean±SEM, box plots present median and quartiles. When analyzing blood pressure during several time points, a 2-way repeated measures ANOVA was used followed by a Holm–Sidak test for individual comparisons when appropriate. Differences were considered statistically significant if $P \leq 0.05$. Statistics used for various microbiome analysis are presented in the online-only Data Supplement.

Results

OSA Synergizes With a High-Fat Diet to Produce Hypertension in Long Evans Rats

OSA (60 apneas/hour for 8 hours during the sleep cycle) for 2 weeks had no effect on blood pressure in 10-week-old rats compared with sham rats (Figure 1A). Similarly, high-fat diet alone (60% total calories from fat for 5 weeks) had no significant effect on blood pressure (Figure 1B). However, when OSA was started after 3 weeks of high-fat diet, blood pressure increased 24 and 29 mm Hg after 1 and 2 weeks of OSA, respectively (Figure 1B). Although body weight was greater in rats on a high-fat diet (393±10 g) when compared with rats on a normal chow diet (376±11 g), the difference was not statistically significant. Note that neither OSA alone nor high-fat diet alone produced hypertension, yet when combined the 2 synergized to produce hypertension.

Figure 1C illustrates that administration of oral antibiotics, a tool often used to alter gut microbiota, prevented the increased blood pressure in rats on a high-fat diet and undergoing OSA. In addition to altering the composition of the gut microbiota (Figure 2A), oral antibiotics dramatically decreases the gut biomass.[16] These data suggested that dysbiosis may play a role in OSA-induced hypertension.

OSA-Induced Hypertension Is Associated With Alterations to the Gut Microbiota

Figure 2A demonstrates the effects of diet, apnea, and antibiotics on the major phyla of the gut microbiota. High-fat diet led to a significant increase in the Firmicutes: Bacteroidetes (F:B) ratio, a well-established signature of gut dysbiosis (Figure 2B).[17] The F:B ratio of OSA rats on a high-fat diet tended to be lower than rats on a high-fat diet alone; however, this was not statistically different (P=0.112). In addition, gut dysbiosis is generally accompanied by a decreased diversity of the bacteria present. The Chao 1 richness index, which takes into account the total number of distinct genera present, was significantly decreased after high-fat diet (Figure 2C). The Shannon index of diversity, which takes into account richness and abundance, was not statistically different between chow and high-fat fed rats. OSA did not alter the Chao 1 or Shannon indices in rats compared with their corresponding sham group. It seems that a major contributor to the gut dysbiosis in our study was high-fat diet.

Figure 3 shows the bacterial taxa (class, order, family, and genus) that were altered by high-fat diet or by OSA, according to LEfSe analysis.[18] Although the goal of our analysis was to classify bacteria to the genus level, the incomplete nature of available bacterial reference databases only allowed us to classify to the level of class, order, or family in some cases. When bacteria could not be classified to the genus level, we report the lowest taxonomic level achieved in that analysis. In Figure 3, the fold change in relative abundance (to the $\log_{10}$) of statistically significant taxa are depicted on the horizontal axis. Prominent changes occurred after a high-fat diet alone (no OSA) where the relative abundances of 11 taxa were increased (black in Figure 3A) and 9 taxa were decreased (white) when compared with rats on a chow diet alone. OSA in rats on a normal chow diet also produced several changes in the microbiota taxa compared with sham rats on a chow diet (Figure 3B). Rats on a high-fat diet and undergoing OSA showed decreases in the relative abundances of 3 taxa when compared with the microbiota from sham rats on a high-fat diet (Figure 3C). However, no single taxon or group of taxa responsible for the increased blood pressure in OSA rats on a high-fat diet was readily apparent at this point in our analysis.

Potential bacterial metabolites involved with hypertension in OSA rats on a high-fat diet were examined using PICRUSt analysis to predict functional gene family abundances using 16S rRNA data. When comparing the microbiota of high-fat OSA compared with chow-fed OSA rats, we determined that multiple steps of the butyrate (ie, butanoate) metabolism pathway were predicted to be downregulated. Most prominent was the predicted decrease in the relative abundance of acetate CoA transferase, the final enzymatic step in butyrate production (Figure S1). Butyrate, a short chain fatty acid (SCFA) produced by bacterial fermentation of dietary fibers in the gut, has been shown to play an important role in maintaining overall gut health.[19,20]

Ruminococcaceae (order Clostridiales) that are prominent producers of butyrate, decreased in relative abundance with a high-fat diet (Figure 3D). This decrease is particularly significant because Ruminococcaceae, making up ≈20% of gut bacteria in chow-fed OSA rats, decreased to ≈10% in high-fat OSA rats (Figure 3D). Members of the order Clostridiales, other than Ruminococcaceae, also significantly decreased with high-fat diet (Figure 3E).

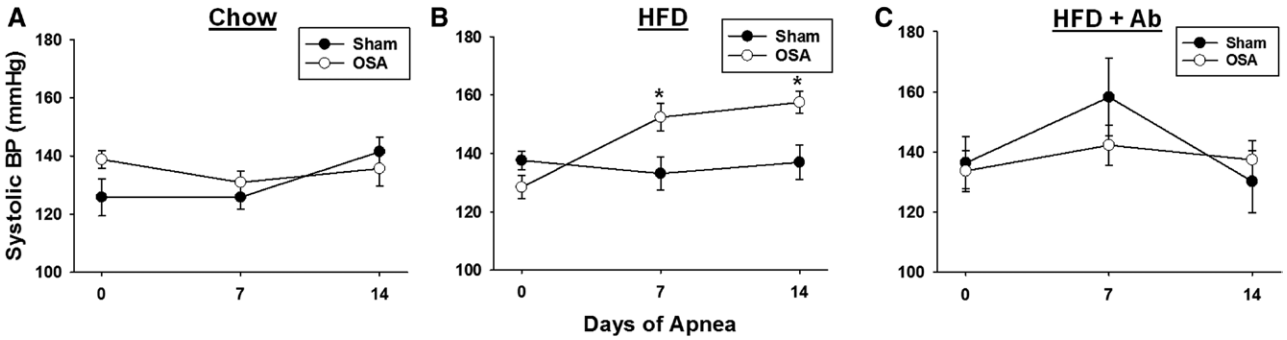

Figure 1. Obstructive sleep apnea (OSA)–induced hypertension requires a high-fat diet. **A**, Sham and OSA rats fed a normal chow diet had no difference in systolic blood pressures (n=4 per group). **B**, On high-fat diet OSA rats exhibited significantly higher systolic blood pressure, when compared with sham rats, after 7 and 14 days of OSA (n=10–13 per group). **C**, OSA-induced hypertension was prevented by oral antibiotic treatment (n=6–9). Data are shown as the mean±SEM, **P*<0.05 for sham vs OSA. Ab indicates antibiotic; and HFD, high-fat diet.

In addition to changes in SCFA producing bacteria, LEFSe analysis demonstrated that the effects of diet and apnea were characterized by many bacteria involved in lactate metabolism, including Lactococcus, Coprobacillus, and Holdemania (Figure 3A and 3C). We observed an increase in the relative abundance of the lactate-producing genus Lactococcus with high-fat diet, that was completely absent on normal chow diet. This genus was unaffected by OSA (Figure 3F).

Hypertensive Phenotype of OSA Rats Is Transferrable Via the Gut Contents

To definitively isolate the role of the gut in OSA-induced hypertension, we transplanted cecal contents from donor rats into the gastrointestinal tract of recipient rats, with the goal of establishing a gut microbiota similar to the donor.[21] Recipient rats, on a normal chow diet, were gavaged with cecal contents from donor sham (normotensive) or OSA (hypertensive) rats on a high-fat diet (Figure 4A). All recipient rats remained on normal chow and underwent 2 weeks of OSA. Recall that OSA rats on normal chow diet do not develop hypertension (Figure 1A). Recipient rats that received the cecal contents from a sham donor on high-fat diet had no change in blood pressure (Figure 4A). However, rats receiving cecal contents from an OSA donor on high-fat diet exhibited a 14 and 32 mm Hg increase in blood pressure at 7 and 14 days of OSA, respectively (Figure 4A).

Examination of the microbiota after 2 weeks of OSA revealed several differences between rats gavaged with normotensive sham versus hypertensive OSA cecal contents. Rats that received cecal transplants from OSA versus sham donors exhibited a significant increase in the relative abundance of bacteria belonging to the family Coriobacteriaceae, which contains numerous genera known to produce lactate (Figure 4B). In

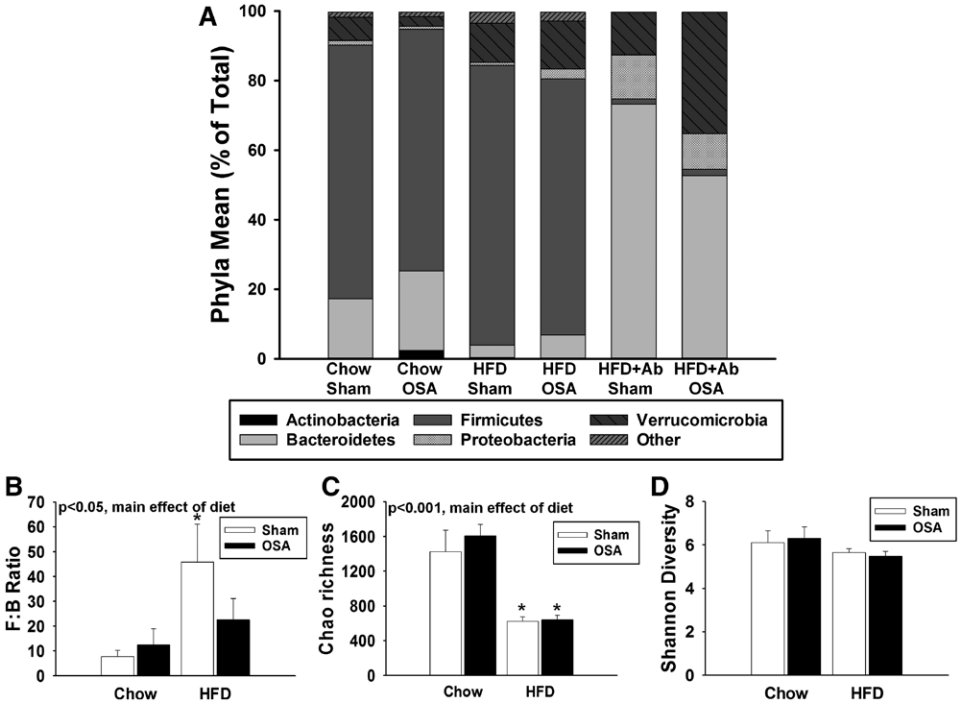

Figure 2. Dysbiosis after changes in diet, obstructive sleep apnea (OSA), and antibiotic treatment. **A**, Relative abundance of the major phyla of the gut microbiota. **B**, High-fat diet increased the Firmicutes:Bacteroidetes (F:B) ratio. **C**, High-fat diet decreased the estimated microbial community richness (Chao1 index). **D**, High-fat diet or OSA did not affect the microbial community diversity (Shannon index). Data are shown as the mean±SEM; n=4–9, **P*<0.05 for high-fat diet sham or OSA vs respective chow groups. Ab indicates antibiotic; and HFD, high-fat diet.

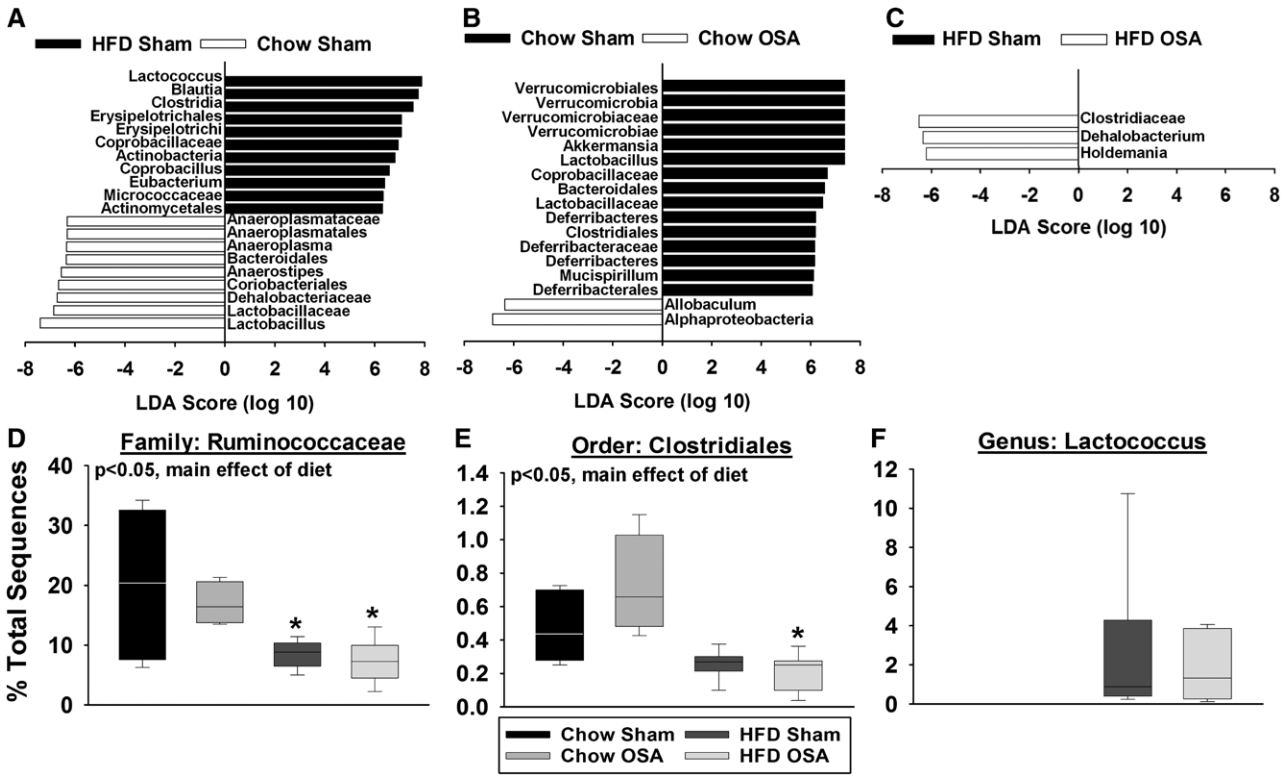

Figure 3. Diet and obstructive sleep apnea (OSA) alter the relative abundance of multiple bacterial taxa. LEFSe analysis was used to identify and calculate a linear discriminate analysis (LDA) score for taxa that characterize (**A**) high-fat diet vs chow-fed sham rats, (**B**) OSA vs sham chow-fed rats, and (**C**) OSA vs sham high-fat fed rats (n=4–7). In **A**–**C**, positive LDA scores indicate the enrichment of taxa in condition 1 (black) relative to condition 2 (white), and negative LDA scores indicate the depletion of taxa in condition 1 relative to condition 2. Given this relationship, the negative LDA scores can also be interpreted as enrichment in condition 2 (black) relative to condition 1 (white). Effects of diet and OSA on (**D**) Ruminococcaceae, (**E**) Clostridiales, and (**F**) Lactococcus abundance. Data are shown as the median and quartiles; n=4 to 7, **P*<0.05 for high-fat diet sham or OSA vs respective chow groups. HFD indicates high-fat diet.

addition, there was a ≈4-fold decrease in the relative abundance of the genus Eubacterium, known to convert lactate to butyrate, in OSA versus sham cecal transplant rats (Figure 4C).[22]

Gavaging cecal contents into naive rats had no effect on blood pressure regardless of whether the donor was sham (normotensive) or OSA (hypertensive) (Figure 4D). These findings demonstrate that gut contents from a rat on high-fat diet and OSA are capable but not sufficient to induce hypertension in a recipient rat, and requires OSA post-transplantation.

Discussion

We provide strong evidence that the gut microbiota plays a key role in the development of hypertension in our rat model of OSA. We report 3 major findings. (1) In our rat model of OSA, a complicating condition, such as that associated with high-fat diet, was required to produce hypertension. (2) Gut dysbiosis, and not other factors associated with a high-fat diet, was involved in the development of OSA-induced hypertension. (3) Gut dysbiosis associated with OSA-induced hypertension involved significant decreases in bacteria involved in butyrate production and increases in bacteria involved with lactate production.

We have previously demonstrated that 2, 4, or 8 weeks of OSA in young healthy Long Evans rats (10 weeks old) does not produce hypertension (D. Durgan and R. Bryan, unpublished data).[14,15] However, we do note that the effect of OSA alone does seem to be strain dependent.[23] In this study, we demonstrated that Long Evans rats require a complicating condition in order for OSA to produce hypertension (Figure 1). The purpose of combining high-fat diet with apneas was to mimic the human conditions where OSA is often accompanied by a complicating condition (obesity, diabetes mellitus, or aging).[1–3] Neither OSA alone nor high-fat diet alone altered blood pressure, yet the 2 synergized to produce hypertension. Of note, a possible synergy between OSA and comorbid conditions in humans is often disregarded.

Although previous studies have provided a provocative correlation between gut dysbiosis and hypertension in rat models and humans, a direct cause and effect relationship had not been previously established.[24,25] Our cecal transplantation studies go beyond an association or correlation, and conclusively demonstrate the involvement of the gut in OSA-induced hypertension (Figure 4). Furthermore, we demonstrate that changes to the gut microbiota result from both high-fat diet and OSA (Figures 3 and 4).

Analysis of the gut microbiota revealed decreased bacteria associated with the production of butyrate, a SCFA, and increased bacteria associated with the production of lactate. The SCFAs, butyrate, propionate, and acetate, are produced by many bacterial species when dietary fiber is fermented in the colon. Each of these SCFAs is beneficial in maintaining gut health and homeostasis. Most prominently, butyrate has been shown to confer cardioprotection, reduce obesity, and improve insulin sensitivity by maintaining gut barrier function, reducing inflammation, and inhibiting histone deacetylation to alter transcriptional regulation.[19] In addition, SCFAs can be absorbed

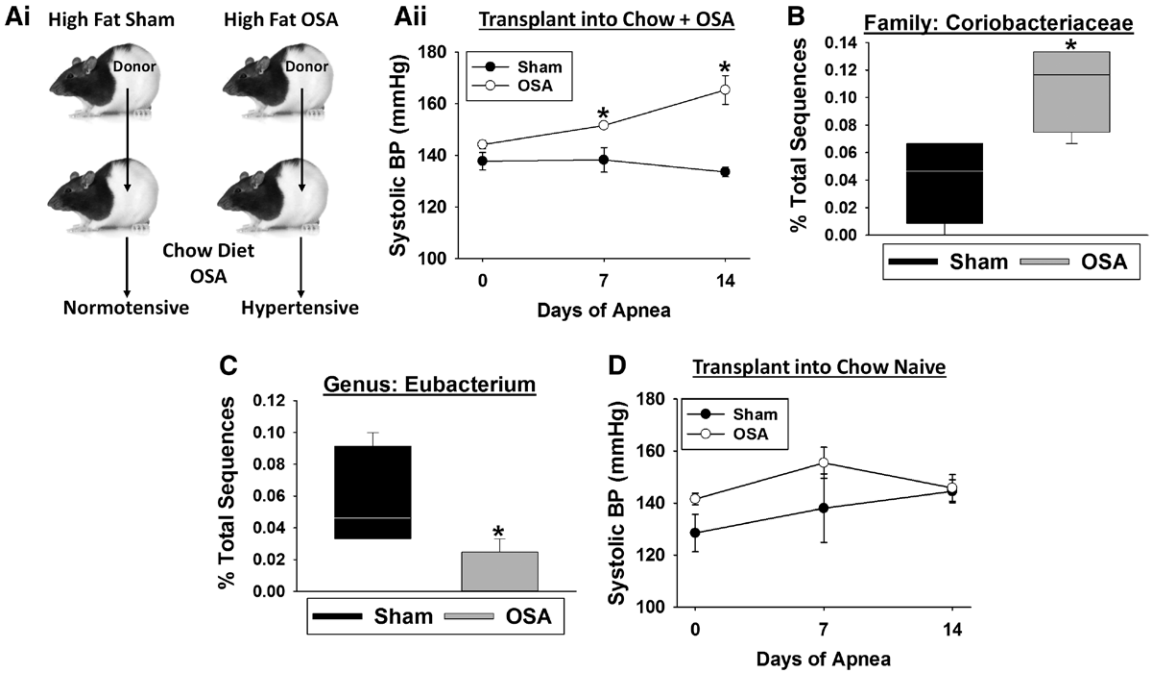

Figure 4. The hypertensive phenotype of obstructive sleep apnea (OSA) rats is transferrable via the gut contents. **A**, OSA recipient rats gavaged with cecal contents from high-fat OSA donors, but not those from a high-fat sham donor, exhibited significant increases in systolic blood pressure after 7 and 14 days of OSA. **B**, Naive recipient rats gavaged with cecal contents from high-fat sham or OSA donors exhibited no change in systolic blood pressure. Effects of high-fat diet sham and OSA cecal transplants on (**C**) Coriobacteriaceae and (**D**) Eubacterium abundance in chow diet OSA recipients. Data are shown as the mean±SEM (**A** and **B**) and the median and quartiles (**C** and **D**) n=4, **P*<0.05 for OSA recipient vs sham recipient.

into the circulation and affect blood pressure through activation of various G protein–coupled receptors in the vascular wall.[16] Our analysis revealed that OSA rats on a high-fat diet (hypertensive) had decreased abundance of multiple butyrate-producing taxa (Figure 3). A decrease in the production of butyrate could destabilize the gut epithelial barrier through mechanisms mentioned above or enhance vascular tone, especially in the kidney, leading to hypertension when the rat undergoes OSA.

Plasma lactate levels are associated with an increase in blood pressure.[26] In our model, high-fat diet led to an increase in the relative abundance of lactate-producing genera Lactococcus and Coprobacillus (Figure 3A and 3F). In addition, we observed a decrease in the family Ruminococcaceae (Figure 3D), which negatively correlates with plasma lactate levels.[27] These findings demonstrate significant alterations to the gut microbiota of OSA-induced hypertensive rats; with an overall decrease in butyrate and increase in lactate-producing bacteria. Similar shifts in butyrate and lactate producers were previously reported for spontaneously hypertensive and angiotensin II rat hypertension models.[24]

In support of the idea that altered microbial butyrate and lactate production contributes to OSA-induced hypertension, similar microbial community shifts were observed after microbiota transplant with decreased butyrate and increased lactate producers (Figure 4). Of note, our studies did not conclusively demonstrate that butyrate or lactate were responsible for the OSA-induced hypertension. However, our studies do provide direction for mechanistic hypotheses examining how dysbiosis synergizes with OSA to result in hypertension. Stimulation of the sympathetic nervous system in the gut compromises gut barrier function, and it is capable of altering the microbiota.[28,29] Importantly, OSA is a powerful stimulus of the sympathetic nervous system.[1] Together the effects of high fat–induced dysbiosis and OSA sympathetic activation may result in further dysbiosis, gut barrier disruption, translocation of gut bacteria or endotoxins, and systemic inflammation, which has been shown to contribute to the development of hypertension in various models.[30]

Perspectives

The gut microbiota plays a critical role in modulating host metabolism, immunity, and inflammation. Studies have linked gut dysbiosis to pathologies beyond the gastrointestinal tract, including obesity, diabetes mellitus, and atherosclerosis. Previous studies have demonstrated an association between gut dysbiosis and hypertension; however, a direct causal relation between the 2 was lacking. We demonstrate that high-fat diet–induced gut dysbiosis is not only associated with, but is an underlying component of OSA-induced hypertension. Our studies demonstrate an important link between gut dysbiosis and blood pressure, and suggest manipulation of the microbiota may hold promise as a treatment of hypertension.

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Disclosures

None.

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Novelty and Significance

What Is New?

- We demonstrate a causal role for gut dysbiosis in the development of obstructive sleep apnea–induced hypertension.
- High-fat diet and obstructive sleep apnea–induced dysbiosis can be characterized by a decrease in butyrate-producing bacteria.
- Cecal transfer experiments demonstrate that gut dysbiosis synergizes with obstructive sleep apnea to induce hypertension.

What Is Relevant?

- Understanding the role of the gut microbiota in hypertension not only contributes to our understanding of the pathogenesis of this prevalent disorder, but also offers a new potential target for therapeutics.

Summary

High-fat diet synergizes with obstructive sleep apnea resulting in a dysbiotic microbiota that is capable of producing hypertension. Methods to prevent or manipulate gut dysbiosis may be beneficial in the treatment of hypertension.