Meds Modify Microbiome, Mediating Their Effects

Nicole M. Koropatkin¹ and Eric C. Martens¹,*
¹University of Michigan Medical School, Ann Arbor, MI, USA
*Correspondence: emartens@umich.edu
http://dx.doi.org/10.1016/j.cmet.2017.08.022

The mechanisms of action of some common medications remain unknown but, in some cases, may involve the microorganisms within us. A new study by Wu et al. (2017) provides evidence that the type 2 diabetes drug metformin alters the gut microbiota, which in turn may mediate some of the drug’s effects.

The trillions of microorganisms that inhabit the human lower gastrointestinal tract collectively encode far more genes than are present in the human genome, including digestive and other physiological functions exclusive to this community (Ku and Gordon, 2003). This metabolic diversity—combined with the fact that most compounds that we ingest interact at some point with gut microbes—creates opportunities for intestinal microbes to modify many foods and drugs. Indeed, recent studies have shown both direct and indirect effects of gut microbes on drug activity, which is often due to the location of these organisms in the small and large intestines and the novel enzymatic activities and metabolites that they produce. For example, the intravenous chemotherapy irinotecan is activated in the human circulation and eliminated by the liver as a glucuronide, producing the primary target of this drug could be gut microbes (Haiser et al., 2013). Finally, some of the typical metabolites produced by gut bacteria enter the host’s circulation and interfere with detoxification pathways used to eliminate ingested drugs, as is the case for microbiobially produced para-cresol and acetalaminophen toxicity (Clayton et al., 2009).

Metformin is a safe and effective treatment for diabetes whose precise mechanism is still unclear, although it inhibits liver gluconeogenesis, thereby lowering blood glucose levels and %HbA1c, a measure of hemoglobin glycosylation due to excess glucose. However, several recent studies support the idea that at least part of metformin’s effect lies in its ability to alter the composition or metabolism of the gut microbiota. The oral availability to the host of metformin is ~50%, meaning that about half of the oral dose directly reaches gut microbes (Song, 2016). A recent study by Fineman and colleagues compared standard metformin with a formulation including an enteric coating that further reduced host availability to 25%, demonstrating that this delayed release pill was just as effective and supporting the idea that the primary target of this drug could be gut microbes (Buse et al., 2016). Additional observations have shown that metformin is more active when taken orally compared to intravenous delivery (Stepensky et al., 2002) and increases the abundance of bacterial species shown by others to improve metabolic syndrome (Shin et al., 2014). Most recently, a new study by Wu et al. (2017) reveals that in type 2 diabetic patients, metformin changes both the composition of the microbiota and that the drug has a direct impact on the metabolism of gut bacteria.

The gut microbiota of diabetics is different from that of healthy people, yet diabetes treatment typically involves dietary changes that can alter the gut microbiota (Clayton et al., 2009). While many foods and drugs alter the composition of the gut microbiota, establishing a direct link between this change and the mechanism of metformin is more difficult. To bridge this gap, Wu et al. (2017) transplanted the fecal bacterial communities from patients who received metformin or placebo into germ-free mice to evaluate whether the altered gut microbial communities exert different effects in a new host. Remarkably, mice that received the microbiota from patients taking metformin exhibited lower blood glucose levels, even though these mice were not exposed to the drug. This finding suggests that the metformin-influenced microbiota retains a metabolic signature outside of its human host that persists and influences a new host’s physiology similarly to the original treatment.

To evaluate the possibility that metformin directly alters the metabolism of gut bacteria, Wu et al. (2017) took fecal samples from two different metformin-treated donors and passaged these with and without metformin in a “gut simulator,” a dual-chambered vessel that mimics the pH and microaerophilic oxygen conditions within the small and large intestines. After culturing, DNA sequencing of the community (metagenomics), as well as mRNA sequencing to evaluate changes in gene expression (metatranscriptomics),
revealed that metformin changes both the bacterial community composition and metabolism. While Wu et al. (2017) note differences in the bacterial taxa between the two cultures following metformin treatment, there was a convergence of the communities toward shared metabolic features. Furthermore, the metatranscriptomics revealed that genes regulated by metformin treatment may be involved in metal uptake and/or metalloprotein synthesis. While this observation does not reveal the precise mechanistic pathway(s) altered by metformin, it further suggests that metformin’s effect is mediated by gut microbes and narrows the list of mechanistic possibilities.

We all harbor a unique microbial community within our guts, and factoring this aspect of our health into an evaluation of how we respond to drugs is likely to become a key aspect of personalized medicine. While metformin is the first line of defense for the treatment of type 2 diabetes, there are individuals for which this medication is insufficient (Hawes et al., 2016), and the reasons may be due to confounding host factors—or the microbial community. As we grow closer to understanding how metformin promotes glucose control in diabetics, it will be key to understand how diet and drugs may be used to enhance the microbiota. In this revealing study by Wu et al. (2017), there is ample evidence supporting the idea that metformin may work for diabetics by selecting bacteria with distinct metabolic features and that these alterations to gut microbes exert an effect that is sustained even after drug removal. From this perspective, it will be interesting to see how long blood glucose control is enhanced following the end of metformin treatment, how the microbiota responds, and what types of diet help sustain functional alterations in gut microbes.

How various drugs, including metformin, change the physiology of the gut community is unclear, and certainly different studies reveal different changes. For example, previous human studies with metformin have noted an increase in a gut mucosal-associated bacterium Akkermansia muciniphila that correlates with enhanced glucose tolerance (Shin et al., 2014), and other work has demonstrated that prebiotic feeding to increase A. muciniphila enhanced blood glucose control in obese and diabetic mice (Everard et al., 2013). In Wu et al. (2017), an increase in A. muciniphila was noted in metformin-treated individuals, but there was no significant correlation with improved glucose control. Rather, increases in other enteric genera, such as Bifidobacterium and Escherichia, which are not typically associated with improvements in glucose tolerance, were noted. Understanding why human studies reveal different results will be key to understanding the many ways in which diet, the microbiome, and host physiology intersect to change our health.

The human gut microbiome is emerging as a major factor in many aspects of human physiology during health and disease. Moving beyond correlative investigations of gut microbes and their effects on food, drugs, and other treatments—many of which inevitably elicit collateral, secondary changes in the microbiota—will require a multi-disciplinary approach.

The investigation by Wu et al. (2017) illustrates one path to move from human studies to animal models and in vitro systems to hone our functional understanding of how our most metabolically diverse organ—our gut microbiota—can be leveraged to promote health.