CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Burning Fat by Bugging the System

Evan D. Rosen, M.D., Ph.D.

Many of us live in a world where nutritional abundance and physical inactivity are the norm; such conditions are antecedents to obesity, type 2 diabetes, and dyslipidemia. The high prevalence of these disorders and the toll they take on our physical, emotional, and economic health have provoked intense inquiry into the physiological mechanisms underlying metabolism. Two areas that have attracted recent attention are the identification and manipulation of brown adipose tissue in humans and the role played by the gut microbiome in energy balance. Although these two research areas have been thought to be separate from one another, new work suggests that there is an intimate relationship between our gut flora and the ability of our fat depots to switch from calorie storage to an energy-burning mode.

Mammals have at least two types of adipose tissue: the familiar (and all too abundant) white fat that stores extra calories, and brown adipose tissue that dissipates energy through mitochondrial uncoupling and the production of heat. A third type of fat cell, called the "beige" adipocyte, has the ability to transition between states of energy storage and dissipation; it has been the subject of intense research interest because of its inherent inducibility and because it has recently been discovered in adult humans.[1] Studies of mice have identified several drivers of the appearance of beige fat cells in white fat pads, a process known as "browning." Most prominent among these driving factors is cold exposure, which works in part through central activation of sympathetic pathways and in part through the local elaboration of catecholamines by macrophages.

Cold-induced browning can promote impressive weight loss in mice, as well as improvements in insulin sensitivity and reductions in hyperlipidemia. Metabolic benefits of cold-induced browning have also been shown in humans; however, people do not particularly enjoy being cold, as evidenced by the invention of clothing, home heating, and winter trips to the tropics. Moreover, "short-circuiting" the need for cold exposure by administering catecholamines is likely to be both ineffective and potentially harmful. Thus, one can understand the impetus to identify new mechanisms that can be exploited to induce browning in a safe and effective manner.

In a recent study, Chevalier and colleagues[2] identified a new and somewhat unexpected pathway linking the gut microbiome to the browning of white fat. We have trillions of bacteria colonizing our bodies, with a particularly high density in the large and small intestine. Advances in large-scale sequencing technology have enabled us to quantify the distribution of bacterial species in our guts and to determine how this is altered by diet. More importantly, there is a burgeoning realization that the composition of the microbiota not only reflects dietary changes but also directly modulates the metabolic function of the host. Thus, altering the microbiome through antibiotic therapy or transfer of specific bacterial genera can affect body weight, insulin sensitivity, and other metabolic measures; how this occurs has been unclear.

The new work shows that cold exposure, like dietary change, provokes alterations in the gut microbiota of mice. Moreover, when cold-adapted flora are transferred to a germ-free animal, the recipient mouse loses fat mass and has improved insulin sensitivity, which is brought about by a process that involves enhanced browning (Fig. 1). In a finding consistent with this observation, mice that receive cold-adapted bacteria (vs. "normal" flora) are better able to defend their body temperature on being placed in the cold. Thus,

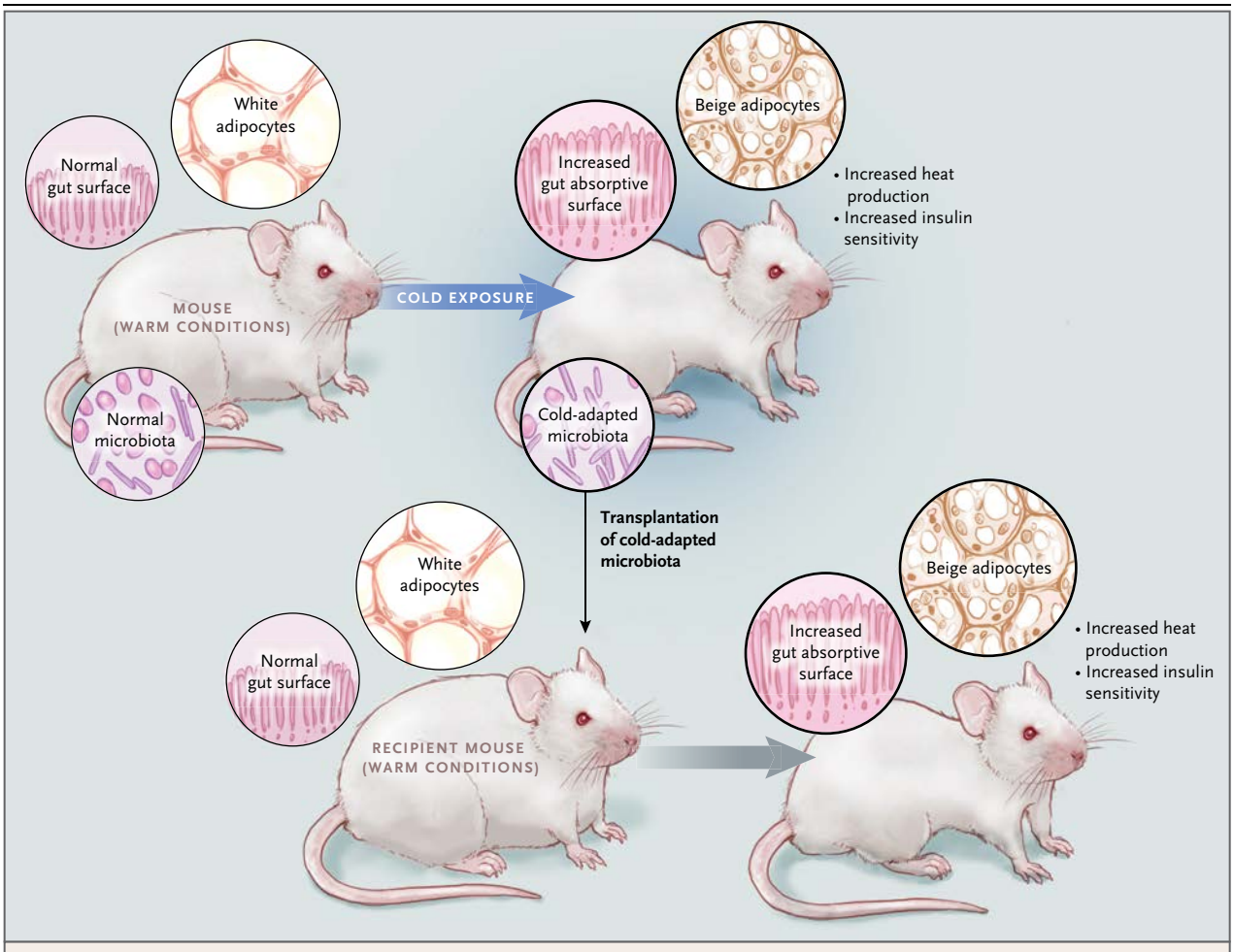

Figure 1. Coming in from the Cold.

Cold exposure causes browning of white fat in mice, with increased insulin sensitivity and heat production in addition to weight loss. Chevalier and colleagues[2] reported that cold exposure also changes the composition of the gut microbiota and causes a large increase in the absorptive surface of the gut. Transplantation of the cold-adapted microbiota from cold-exposed mice is sufficient to promote browning, enhanced insulin sensitivity, and increased intestinal surface area in warm recipient mice.

diet is not the only environmental factor being monitored by the microbiome. Furthermore, these results suggest that the effect of cold on beige fat recruitment may be relayed, in part, through our intestinal flora.

Continued cold exposure does not cause an animal to waste away, of course; a new balance is established between continued fat loss and fat accretion. To provide fuel for highly thermogenic brown fat, this steady state must be characterized by increased food intake — which certainly occurs — or by enhanced nutrient absorption. This new work shows that prolonged cold exposure induces a massive increase in the absorptive surface of the gut, in association with reduced apoptosis of the cells making up its microvilli. Once again, this effect could be achieved simply by transplanting cold-adapted gut microbiota to germ-free hosts. Taken together then, remodeling of the intestine and adipose tissue are coordinated during cold exposure, and both processes are promoted by changes in the microbiota. The increased browning of white fat happens first, followed by an increased absorptive surface in the gut, a process required to keep the furnace fueled.

Which specific components of the microbiota mediate this effect? The authors show that cold causes a profound increase in the ratio of Firmicutes to Bacteroidetes, as well as almost a

complete loss of Verrucomicrobia species, including *Akkermansia muciniphila*; such changes have been noted previously in mouse models of obesity and are associated with increased energy extraction from food.[3] When *A. muciniphila* was added back to the cold-adapted flora, the effect of cold on increased gut absorption was blocked. However, the effects on browning and insulin sensitivity were not altered by replenishment of *A. muciniphila*. Previous work has shown that *A. muciniphila* promotes leanness and increases energy expenditure in mice, inducing a gene expression pattern in adipose tissue suggestive of increased fatty acid oxidation (as would occur in browning).[4] Thus, the precise role of akkermansia in energy balance is complex, and the specific identity of the pro-browning flora that are activated by cold remains obscure.

There are additional issues to consider before adding obesity and insulin resistance to the list of diseases that may be amenable to probiotic therapy or fecal transplantation. A companion article from the same group suggests that antibiotic therapy, which depletes the gut microbiota, also induces browning and weight loss.[5] This finding may go a long way toward explaining the observation that germ-free mice are lean and highly resistant to diet-induced obesity. Nonetheless, it is not a straightforward exercise to integrate these findings with the results showing that cold-adapted microbiota promote browning. Furthermore, antibiotic therapy is associated with increased body weight in animals and humans, although it is possible that the specific antibiotic treatment used by Suárez-Zamorano and colleagues[5] spares a pro-browning bacterial species in the treated mice; alternatively, the timing and duration of the treatment may be of critical importance in determining the ultimate outcome of antibiotic therapy with regard to adiposity. There is also the overarching question of whether enhancement of browning in humans is a viable therapeutic strategy; early efforts in this area have produced mixed results that have not been as uniformly impressive as those seen in studies of rodents.

Still, this recent work shows that we have a lot to learn about the gut microbiome and about how to incorporate it into our thinking about organismal metabolism. Furthermore, we are provided with an example of how multiple organ systems (in this case, adipose tissue and the gut) together maintain an overall homeostasis in the face of an environmental challenge. The accessibility of the gut renders it an attractive tract for experimental approaches to treat obesity and type 2 diabetes; further studies should reveal how tractable it truly is.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Division of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical Center and Harvard Medical School — both in Boston.

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