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Antibiotics in early life and obesity

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Abstract

The intestinal microbiota can influence host metabolism. When given early in life, agents that disrupt microbiota composition and consequently its metabolic activity, can influence body mass of the host by either promoting weight gain or stunting growth, which is consistent with effects of the microbiota on development. In this Perspective, we posit that microbiota disruptions in early-life can have long-lasting effects on body weight in adulthood. Furthermore, we examine the dichotomy between antibiotic-induced repressed or promoted growth and review the experimental and epidemiological evidence that supports these phenotypes. Considering the characteristics of the gut microbiota in early life as a distinct dimension of human growth and development, as well as comprehending its susceptibility to perturbation, will allow for increased understanding of human physiology and could lead to development of interventions to stem current epidemic diseases, such as obesity and types 1 and 2 diabetes mellitus.

Introduction

The human body is host to a vast number of microbes, including bacterial, fungal and protozoal cells, which are present in far greater number than human cells and collectively constitute our microbiota. Together with their parasitizing, or perhaps commensal viruses, these microbes carry out numerous functions important to human biology, such as aiding in the development of immunity, protecting against invading pathogens, synthesizing essential vitamins and extracting nutrients from food. The composition of the microbial community is shaped by multiple factors including the genotype and immunity of the host, as well as environmental influences, such as diet, therapeutic agents, and direct transmission of microbes through person-to-person contact or transmission through the air, drinking water, or food and utensils. The composition of these microbial communities is dynamic and the microbiota is subject to both minor and major disturbances, such as infection, exposure to antibiotics and major dietary shifts.^{1,2}

Transmission (from mother to child), establishment and maturation of the infant intestinal microbiota is a choreographed process that begins in pregnancy (Table 1) and can be

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perturbed by treatment with antibiotics, changes in diet and interruption of vaginal transmission.³ Moreover, it seems that the microbiota has increased susceptibility to perturbations at some stages of life, particularly during infancy, which is a time before a stable microbial community has developed.⁴ Infants acquire much of their founding microbiota at birth (Figure 1), and these microbial populations subsequently undergo maturation over the next several years. A microbiota with adult-like complexity is developed by 3 years of age,⁵ which corresponds to the age where infants transition to consumption of a diet similar to that of adult individuals and corresponds with development of major components of acquired (adaptive) immunity.⁶ In the first year of life, the microbiota has a beneficial role in shaping healthy host development; however, altered microbiota have also been associated with negative outcomes at later stages in life, such as obesity in juvenile individuals.⁷ Additionally, breastfeeding has an important role in the selection of microbiota;⁸ milk components can be differentially digested to provide nutrient sources for health-promoting microbes, such as *Bifidobacterium* and *Lactobacillus*. That microbiota composition is host-specific⁹ and conserved within many mammalian species suggests their importance throughout evolutionary time (>100 million years), and is consistent with an optimal development of host-microbiota interactions choreographed by shared early-life behavioural and physiological characteristics, including mode of birth, breast feeding, and close interaction with neonatal offspring. Adoption of medical advances, such as Caesarean sections, antibiotics and formula feeding might contribute to perturbations in the ancient processes that dictate host-microbiota interactions.

The compromising effects of antibiotics on the important function of the microbiota to mediate colonization resistance has been reviewed extensively elsewhere.¹⁰ An appreciation for the contribution of antibiotic-induced microbiota disturbances to metabolic changes in the host is emerging. Several studies have established that the intestinal microbiota can modulate host metabolism;¹¹⁻¹³ it is, therefore, plausible that agents that specifically modulate the microbiota, such as antibiotics, can affect body weight. In this Perspective, we discuss critical time points in the development of microbiota–host interactions, the sources of early-life microbiota disruption and provide a commentary on future research directions.

Antibacterial exposures

Patterns of microbial colonization in early life can be disrupted by altering the composition of founding microbial populations and/or through infant exposures to antibiotics. Maternal antibiotic exposure is a relevant consideration, as infants acquire at least a part of their early life microbiota from their mother. Antibiotic exposure immediately prepartum, as occurs in more than 30% of US women to prevent Group B *Streptococcus* infection¹⁴, could have a direct effect on the vertical transmission (which occurs from mother to child during pregnancy or childbirth and after) of microbiota. However, the effects of antibiotic exposures in early pregnancy, or even prior to pregnancy, on maternal transmission of microbiota to infants has not been established. Additionally, between the first and third trimester, there are conserved shifts in maternal microbiota composition,³ which might confer evolutionary advantages for fecundity and infant survival and it is possible that these changes are also subject to disruption with antibiotics. Our group has postulated that maternal exposure to antibiotics could affect intergenerational transmission of microbiota.¹⁵

A large population-based Danish study reported that 78% of mothers received an antibiotic in the cumulative 4 years before, during and after pregnancy; of these women, 51% had received three or more courses of antibiotics during the study period.¹⁶ Interestingly, the likelihood of a child developing asthma was increased when the number of courses of antibiotics taken by their mother increased, with an overall increased risk of 30% in children of the mothers who used antibiotics. One interpretation of these findings is that maternal antibiotic use has a direct effect on the microbiome and physiology of infants, even after birth. Another examination of a cohort of Danish women showed that more than 40% received an antimicrobial agent at least once during pregnancy.¹⁷ In addition to disrupting the transmission of the microbiota from mother to child, prenatal antibiotic exposure has been shown to have effects on birth weights of neonates and is associated with increased risk of obesity and related metabolic sequelae later in life.^{18, 19}

In the USA, infant exposure to prescribed antibiotics is substantial. Analysis of antibiotic prescription rates in 2010 from a database containing information on more than 70% of U.S. prescriptions²⁰ demonstrated widespread antibiotic use, especially during infancy and childhood, that varied substantially by region. Our extrapolation of the data suggests that by the age of 2 years, on average a child in the USA has received nearly three antibiotic courses (largely to treat acute infections of the ears and upper respiratory tract), about ten courses by the age of 10 years, and ~17 courses by 20 years of age. Although these rates are astonishingly high, they are consistent with prior national surveys.^{21, 22} By contrast, in Sweden, antibiotic use from infancy through adulthood is ~40% of that in the USA.²³ This dichotomy suggests that much of the prescribed antibiotic use in US children is unnecessary — a fact which is widely acknowledged by professional bodies; including the American Academy of Pediatrics²⁴ and the Centers for Disease Control and Prevention.²⁵ However, the rates of pediatric antibiotic use in the USA has decreased from 2000 to 2010.²⁶ The US national data also indicate that there are regional differences in antibiotic prescription rates, with higher rates in the south than in the west of the country.^{20, 27} Even within a single region, there is also considerable variation of prescribing amongst doctors, as indicated by a recent large survey of practices associated with a major academic medical center.²⁸

US infants could potentially have substantial exposure to antibacterial agents from other sources, such as through the food supply chain or through drinking water.²⁹⁻³¹ Given that antibiotics are widely used for promotion of growth in livestock, it is possible that meats and milk from these animals might be contaminated with trace residues of these agents.³² However, there are stringent regulations in place in the USA that aim to limit these types of exposures.^{29, 33} Concerns that use of antibiotics in livestock promotes the emergence of antibiotic-resistant bacterial strains that adversely affect human health are longstanding.³⁴ Moreover, emerging studies have drawn attention to the question of whether there also could be direct metabolic effects on health resulting from consumption of contaminated products.^{29, 35, 36}

The overall risk of exposure to antibiotics via contaminated meat and dairy might be related to variations in global regulatory and testing policies.³² Increased levels of exposure might result from ingesting meat, dairy and egg products imported from countries with less stringent regulations than in the USA. Use of subtherapeutic doses of antibiotics is permitted

for meat production in the USA, although the FDA regulates the type of antibiotics used³⁷ and, in theory, the allowable levels of residues in meat. In December 2013, the FDA revised the policy to ask for voluntary withdrawal of antibiotics for growth promotion³⁸, which may further curtail unwanted antibiotic exposure if the policy proves to be effective.³⁹ In 2011, of 5,006 meat samples tested by the FDA from a variety of animals, 47 had detectable levels of antibiotic residues and eight samples had levels above the allowed limit;³³ increased levels of antibiotic contamination were also reported in surveys conducted prior to 2011. Rapid screening methods for sulfonamide detection introduced in 1984 allowed farmers to determine whether calves were above the allowable limit, thus needing a longer wash out period, or were within acceptable limits; this measure decreased samples above the violation limit from 5% to 2% in just 18 months.⁴⁰ Meat from farmed fish also frequently have antibiotic residues detected, raising the concern that practices in aquaculture also could introduce antibiotics into the human food chain.⁴¹

In some US communities, having municipal water intake downstream of farm effluents might lead to potable water having trace levels of antibiotics.³⁰ These exposures could affect the health of infants either directly or through consuming their mothers' milk. Extensive washing and bathing of infants with antibacterial soaps and the ingestion of antibacterial preservatives in food might also contribute to an altering the early life microbiome, possibly in synergy with the disruptive effects associated with Caesarean section births and prescribed antibiotics. Although implementation of hygiene practices that prevent serious bacterial infectious disease, which avoid the need for antibiotics, might be beneficial, it is unclear to know where to set the limit. The extent to which these non-medical exposures influence development of the early life microbiome, as well as their consequences on health later in life are currently unknown but are important topics for future research.

Antibiotics and metabolism

Approximately 70 years ago, veterinary scientists showed that adding low (subtherapeutic) doses of antibiotics to the food or water of livestock resulted in promotion of growth.⁴² This effect has subsequently been shown in common types of mammalian livestock (cows, pigs and sheep) and in poultry.⁴³ A wide variety of antimicrobial agents has been demonstrated to have these effects regardless of class of drug (antibiotic, ionophore, or antiseptic), chemical structure, mode of action and spectrum of activity.⁴⁴⁻⁴⁶ Importantly, when animals are exposed to antibiotics early in life, the effects on both growth promotion and feed efficiency (the ability to convert food calories into body mass) are greater than if the exposure occurs later in life.^{44, 46} The effects associated with age are consistent with the concept of a critical developmental period for shaping host metabolism, with early life being more vulnerable to change than later in life. Antibiotic-mediated promotion of growth is widely practiced by farmers because it is very effective. Studies in germ-free chickens have shown that antibiotics alone have no growth-promoting effects,⁴⁷ providing evidence against a direct effect of antibiotics on host tissues, but rather that the effects are driven by changes in the microbiota of treated animals.

Together the findings from observations and experiments in livestock and poultry indicate that early life is a critical time for metabolic development of the host, there is a role for the

microbiome in this process and that antibiotic exposure in this time affects the course of development.

Evidence from animal models

Several studies have shown that the intestinal microbiota influences host metabolism,^{11, 12, 48} supporting the concept that agents which modulate commensal microbial populations can affect weight of the host (Table 2). Experiments in animal models have provided direct evidence that supports the findings from the early studies in farm animals that suggested a link between treatment with low doses of antibiotics with growth promotion.⁴³ Studies in mice using multiple types of antibiotics have further confirmed this association,⁴⁹ as well as identifying early life as the key period for microbe-mediated programming of host metabolism.⁵⁰ One hypothesis that emerged from the farm posits was that use of antibiotics leads to growth promotion by reducing infection, however, the antibiotic-mediated effects on metabolism were also observed in mice that were reared in specific pathogen-free conditions.^{49, 50} Furthermore, given that the low doses of antibiotics administered in the farm setting are well below therapeutic levels, it is unlikely that these treatments would be sufficient for clearance of pathogens.

Administration of low doses of penicillin or oxytetracycline has been shown to lead to weight gain in mice, but high doses resulted in weight loss.⁵¹ Treating mice with subtherapeutic doses of penicillin, vancomycin and chlortetracycline led to increased fat mass and increased levels of short-chain fatty acids in these animals, suggesting that the altered microbiota had an enhanced metabolism that could drive induction of downstream hepatic genes involved in lipogenesis.⁴⁹ Different antibiotic treatment regimens target specific populations of bacteria. Penicillin (a β -lactam antibiotic) and vancomycin (a glycopeptide) both inhibit cell wall synthesis in Gram positive organisms; chlortetracycline, which inhibits protein synthesis, has very broad spectrum activity.²⁶ Increases in fat mass were seen in all mice treated with antibiotics, regardless of the antibiotic class, which is consistent with findings from studies conducted in farm animals.⁴³ Additionally, in the agricultural setting, efficacy of a wide range of antibiotics, including diterpenes, lincosaminides, macrolides, oligosaccharides, peptides, streptogramins, phosphoglycolipids, polyethers, quinoxalines, and sulfonamides, has been observed.⁴⁴ That treatment with a wide array of antibiotic classes results in increased fat mass and that treatment with antifungal agents does not, suggests that generalized disruption of the gut microbiota can alter host metabolism.

Furthermore, mice that received low-dose penicillin (LDP) treatments at birth had greater increases in total body weight compared to their counterparts that were exposed to LDP at weaning and to control mice,⁵⁰ indicating that early life is a metabolically vulnerable stage. Challenging the mice that received LDP at birth with a high-fat diet accentuated the antibiotic-mediated metabolic effects, demonstrating synergy between the effects from early-life microbiota disruption and dietary excess. Importantly, these metabolic effects lasted into adulthood even after the treatment with antibiotics was terminated. Mice that received LDP for only 4 weeks after birth developed elevated weight and increased fat mass in adulthood starting at 20 weeks.⁵⁰ This effect was not a result of a sustained dysbiosis; 4

weeks after penicillin treatment was stopped, the microbiota had recovered; however, the mice still developed adult-onset obesity. These findings demonstrate that even transient perturbation in the early-life period in which the microbiota contribute to normal development can have long-term effects. Additionally, the altered microbiota itself was capable of producing the obesogenic effect; young (3-week old) germ-free mice that were colonized with microbiota from LDP-treated mice gained more weight and fat mass than mice colonized with microbiota from control animals. Throughout these experiments, there were consistent reductions in population size of specific microbiota, such as *Lactobacillus*, *Allobaculum*, Rikenellaceae, and *Candidatus Arthromitus* (otherwise known as segmented filamentous bacteria, SFB), suggesting that bacteria of these taxa might have protective roles in shaping adult metabolism.⁵⁰

One specific interaction affected might be microbial guidance of the development of intestinal immunity; reductions in intestinal defense can lead to metabolic aberrations.⁵²⁻⁵⁵ Treatment of mice in early-life with LDP or colonization with microbiota from LDP-treated mice resulted in decreased expression of genes in the ileum, which are involved in regulating multiple functions associated with development of innate and adaptive immunity, including antigen presentation, generation of a type 17 T helper (T_H17) cell response and antimicrobial peptides. One population of bacteria that was reduced as a result of LDP treatment was *Candidatus Arthromitus* (also known as segmented filamentous bacteria; SFB), which stimulate T_H17 responses and antimicrobial peptide secretion.⁵⁶ Experiments performed in mice⁵⁷ and limited evidence from studies in humans⁵⁸ have shown that high levels of SFB are present in infancy and that these levels are reduced in adulthood and completely lost after penicillin exposure.⁵⁹

We believe that other organisms have important functions in the ileum, however, SFB is considered a model organism with levels that peak in infancy and that can guide developmental outcomes, as evidenced by loss of this population in early-life having adverse consequences. Other populations within the microbiota also drive development of specific immune outcomes. For example, presence of *Clostridia* species from clusters IV and XIVa can result in an increase in the numbers of lamina propria regulatory T (T_{REG}) cells, which secrete the anti-inflammatory cytokine IL-10. *Bacteroides fragilis* strains that contain polysaccharide A (PSA) also induce mucosal IL-10 secretion, which highlights the importance of specific cell wall components in this process.⁶⁰ Presence of both of these organisms in the microbiota can also modulate systemic immunity; colonization with a cocktail of *Clostridia* species from clusters IV and XIVa resulted in decreased circulating levels of IgE after challenge with a presensitized antigen,⁶¹ and colonization with a PSA-positive *B. fragilis* strain increased numbers of circulating type 1 T helper (T_H1) cells.⁶² Further studies are warranted to investigate the individual mechanisms by which key early-life members of the microbiota shape host immunity.

Many studies have shown that early-life is a critical time for host metabolic development; however, research has also shown that exposure to high doses of antibiotics early in life can stunt growth and lead to underdevelopment⁵¹ or ameliorate metabolic outcomes when animals are challenged with a high-fat diet.^{52, 63, 64} In rodent models of obesity, high doses of antibiotics, which resulted in multilog reductions in numbers of anaerobic and aerobic

bacteria, considerably decreased body weight and/or fat mass and improved markers of insulin sensitivity.^{52, 64, 65} Thus, it seems paradoxical that some exposures to antibiotics can lead to weight loss,^{51, 52, 66} yet others result in weight gain,⁴⁹⁻⁵¹ and some exposures have no direct effect on weight.⁶⁷ Antibiotic exposures that either increase or decrease body weight might differentially alter feeding behaviours⁶⁷ or metabolic signaling, which are factors that can be altered during the early-life developmental period.⁶³ These divergent phenotypic outcomes might explain why the effects of antibiotic treatments on weight remained largely unnoticed in clinical practice, whereas the growth promotion induced by subtherapeutic doses of antibiotics was recognized by farmers decades ago.⁴³

Variations in metabolic outcomes seem to be largely dependent on the dose of antibiotics, timing, mouse strain and diet; the opposing effects on body weight might depend on the overall magnitude of disruption to the microbiota (Figure 2). The intestinal microbiota contribute to host calories by extracting energy from the diet,¹² and loss of microbiota (as in germ-free mice) results in abnormal host metabolism, physiology and immunity. Germ-free C57B/L6 mice weigh less than their conventional counterparts despite similar food intakes. These mice also resist weight gain when exposed to either a western⁶⁸ or high-fat diet,⁶⁹ as a result of decreased energy extraction and altered expression of genes related to energy homeostasis (such as *Fiaf*, the fasting-induced adipose factor).⁵⁰ However, this effect is not universal and might be influenced by factors such as host genetics and diet composition, as germ-free CH3 mice have increased weight gain when exposed to a high-fat diet and reduced fat mass when fed a western diet.⁷⁰ Treatments with antibiotic regimens that produce marked population reductions might create conditions that parallel the germ-free state or could lead to undernutrition.^{51, 52, 64, 65} These effects were magnified when mice were fed a diet was deficient in specific nutrients, such as essential amino acids, and the weight reduction effect was lost when mice were fed a complete diet.⁵¹

Epidemiologic evidence

Emerging epidemiological studies have tested the hypothesis that exposure to antibiotics in early life is associated with increased risk of excess adiposity. In a study of over 28,000 mother–child pairs from the Danish National Birth Cohort,⁷¹ antibiotic exposure in children during the first 6 months was associated with an increased risk of being overweight at 7 years of age, especially for children with mothers of normal weight compared to mothers who were overweight; the effect was stronger in boys than in girls. These findings were supported by those from the Avon Longitudinal Study of Parents and Children (ALSPAC), which included over 10,000 children.⁷² In the ALSPAC birth cohort, when all known confounders were controlled for, antibiotic use in the first 6 months of life was associated with increased BMI at 10, 20, and 38 months of age, which was consistent with the strong effects of exposures to antibiotics in early life seen in farm animals. The Danish and the ALSPAC studies also determined that maternal BMI was a contributing factor for the development of obesity follow exposure to antibiotics in early life, with increased effects seen in children with mothers of normal weight compared to mothers who were overweight. In studies of Canadian infants, antibiotics administered in the first year of life increased the likelihood of a child being overweight at 9 years and 12 years of age, as well as having elevated central adiposity (a marker of metabolic syndrome).⁷³ These effects were observed

after adjustment for other factors known to influence body weight, such as diet, physical activity, having siblings and maternal smoking during pregnancy. Strong sexual dimorphism was apparent, with the effect being almost entirely in male children. A longitudinal study in the USA also showed an association between early life antibiotics and childhood obesity, which was increased with early exposure and multiple treatment courses.⁷⁴ Interestingly, these effects were considerably associated with use of broad spectrum antibiotics, but not with narrow spectrum antibiotics. Finally, in a global cross-sectional study, antibiotics in the first year of life modulated body weight in children, and changes in both directions (increases or decreases) were dependent on both site and country, with an overall association with increased risk of being overweight at 5–8 years of age in boys.⁷⁵ In the same study, the weight gain or weight reduction observed in female children was dependent on the study site, however, overall, no statistically significant effects were observed in these participants. Together these epidemiological studies provide evidence that exposures to antibiotics very early in life (that is in the first year of life) could affect the risk of excess adiposity later in life, which implies that these effects occur during a critical developmental period. The gender-specificity of these effects, if sustained, remains unexplained.

Colonization of an infant relies on vertical transmission from the mother at the time of delivery; thus, maternal exposure to antibiotics or an altered delivery route could also affect microbiota establishment and consequent effects on weight gain. A study of 436 mother–child pairs found an 84% (33–154%) increased risk of obesity at 7 years of age if the mother received antibiotics in second or third trimester of pregnancy.⁶⁰ Increased risk of obesity or being overweight has been associated with delivery by Caesarean section in several independent studies.^{60, 76, 77} These studies provide evidence that transmission of maternal microbiota is likely to be a critical factor that shapes metabolic development in children.

Therapeutic intervention

Administration of probiotics to mothers in the last month of pregnancy in humans,⁷⁸ or in early life in animal models,⁷⁹ results in either increased or decreased growth and weight of offspring, possibly depending on the strain of probiotic and host species. Nevertheless, these studies support the idea that specific populations within the microbiota can influence weight. Additional studies are needed to determine whether probiotics can influence host growth and development following antibiotic therapy.

Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host".⁸⁰ These agents can be purchased without a prescription in many countries and can be used without the requirement of a specific health need. Following antibiotic treatment in the clinical setting, we believe the terminology—targeted restoration bacteriotherapy—helps to delineate future strategies for improving health outcomes that result from disruption of microbiota in early-life. Currently available probiotics are limited to a relatively small number of phylogenetic lineages compared with the highly diverse microbiota in the developing infant and adult individuals; thus, the need to identify additional bacterial therapeutic targets remains unmet. Moreover, the idea of restoration following treatment with antibiotics (to replace what is lost) should be the guiding principle; administration of bacteria might not be required in an individual who does

not have an obviously antibiotic-affected microbiota. Lastly, the term bacteriotherapy⁸¹ highlights the aim of counteracting a disease, and in the case of early-life antibiotic exposure, would be considered a preventive measure. We believe that differentiation of these terms will direct the careful study of clinical outcomes in the future, but given that the field is nascent, much remains to be learned.

Concluding remarks

The assembly of the intestinal microbiota is choreographed with normal human growth and development.⁸² In healthy individuals, the gut microbiome is resilient and able to form stable communities that maintain particular compositional and functional characteristics across generations of individuals. Across the human population, the gut microbiota forms a community structure that is unique compared to oral or skin microbiota, which indicates that there are active forces (including pH, immunity, specific nutrients, limited oxygen, a high flow rate and microbe-microbe interactions) that select for specific states, which drive resilience and recovery following environmental perturbations. Despite homeostatic mechanisms, antibiotic treatments can lead to long-term alterations in microbiota composition,⁸³ resulting in changes to host metabolic functions⁶³ particularly during development.⁵⁰

Our work has demonstrated lasting metabolic consequences from transient disruption to microbiota in early-life despite eventual recovery.⁵⁰ With the aim of reversing some of the metabolic consequences resulting from treatment with antibiotics, strategies to restore microbiota might need to account for the timing of interventions. If the recovery to equilibrium could be accelerated, is it possible to prevent later metabolic sequelae? Importantly, mice treated with penicillin for the first 4 weeks of life showed delayed, but eventual, recovery of microbiota populations; nevertheless, they developed elevated fat mass weeks after microbiota recovery.⁵⁰ The sensitivity of host-metabolic development during this period might indicate that restoration of microbiota immediately following treatment with perturbing antibiotic therapies could be an important preventive measure.

Ultimately, antibiotics are important and potentially life-saving drugs that have considerably reduced the rates of human mortality and morbidity. Although these agents were thought to have minimal long-term metabolic side effects, we are now gaining clear insights to how these microbiota-modulating agents could contribute to obesity. By understanding the metabolic costs associated with these treatments, we can factor them into the equation of clinical guidelines and decisions to continue to support the prudent use of antibiotics.

There are many unanswered questions that warrant research to eventually permit the translation of these findings summarized here to the generalized human population. Additional longitudinal studies in humans that better specify antibiotic exposures (such as dose, class and timing) could help assess the risks associated with use of these drugs. We must increase the understanding of the extent of perturbation required to elicit metabolic effects, as compounded disruptions can have unexpected or magnified effects.⁸⁴ Finally, little is known about the potential to reverse metabolic effects from microbiota disruption in

early life and targeted restoration bacteriotherapy administered at the right time could be beneficial.

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Figure 1. A model of microbiota transmission, maturation and perturbation in the first years of life and possible effects on weight

New born infants receive much of their initial colonizing microbiota at birth. Founding bacterial communities are transferred from the mother's vagina and perineum at birth, through skin contact and consumption of breast milk during nursing, and via skin and oral contact with general care and maternal interaction. The microbial communities may be affected before initial colonization by maternal antibiotic use or by circumventing normal colonization routes (for example, Caesarean-section delivery). The infant microbiota undergoes maturation and increases in diversity and stability, resembling the microbiota of adult individuals by the age of three years.⁵ As a result of its instability, the microbiota in infancy is particularly vulnerable to antibiotic disruption, and having an altered microbiota can effect growth and development later in life. Based on the evidence that the microbiota can participate in metabolic signalling and nutrient extraction, perturbations in their early-life populations may result in divergent metabolic outcomes, including excessive weight gain or stunted development. In theory, it is likely that these disruptions must pass a threshold to exert an effect, and a limited perturbation with rapid recovery might not result in altered weight or adiposity. The microbiota-induced metabolic changes are layered on top of other factors that also can have a strong effect on metabolic development, including genetic predisposition, gender, diet, physical activity, disease, or environmental toxicants.

Figure 2. Proposed pathways of antibiotic-mediated weight modulation

Exposures to high-dose antibiotics that cause extensive and sustained reductions in microbiota populations early in life can stunt growth and lead to underdevelopment.⁵¹ The intermediate steps could involve altered immunological signalling or decreased production of microbiota-derived calories and nutrients—a weight loss effect that is enhanced when the diet is deficient in essential amino acids that can be contributed by the microbiota. Antibiotic treatments in early life that alter microbiota composition, but that have limited effects on the overall microbial population size, can lead to weight gain—potentially by reducing key metabolically protective microbiota species, increasing productions of microbiota-derived calories (such as short-chain fatty acids), altering hepatic function and levels of circulating metabolic hormones or by altering intestinal defences (lowering energy costs). In these divergent scenarios, the disturbance to the microbiota would likely need to exceed a threshold beyond a mild-perturbation of short duration to yield a clinical phenotype.

Table 1

Choreography of microbiota transmission, establishment, and maturation

Stage	Key microbiota components	Sources of perturbation [*]
Pregnancy	Increase levels of lactic acid bacteria in the third trimester ³	Maternal antibiotics ⁸⁵
Birth	Transmission of vaginal microbiota, <i>Lactobacillus</i> , <i>Bifidobacterium</i> and <i>Streptococcus spp.</i> , followed by rise of members of Enterobacteriaceae ⁸⁶	Caesarean-section ⁸⁷ Antibiotic treatment at delivery ⁸⁸
Nursing	Predominance of <i>Bifidobacterium</i> and <i>Lactobacillus spp.</i> ⁸	Formula feeding ^{8, 89} Antibiotic treatment ^{4, 86}
Solid foods	Increase in obligate anaerobe populations (for example, <i>Clostridium</i> and <i>Bacteroides spp.</i>) ⁸⁹	Antibiotic treatment ⁴ Sanitizers

^{*} The sources of perturbation may be cumulative with additive or progressive disruption from multiple insults (such as antibiotics, altered modes of delivery, or lack of breast feeding).

Table 2

Experimental evidence of the effect of antibiotics or disrupted microbiota on host weight

Strain or species	Treatment	Dose	Timing	Diet	Effect on weight	Effect on microbiota	Reference
C57BL6J mice	Germ-free	NA	Lifelong	Western	Less weight gain than similarly fed conventionalized mice	Absent	Backhed ⁶⁸
CH3 mice	Germ-free	NA	Lifelong	Chow	No change	Absent	Fleissner ⁷⁰
				HFD	Greater weight gain		
				Western	Less fat gain		
Germ-free chickens	Penicillin	45.5 mg/kg diet	From birth	Chow	No effect on weight in germ-free chicks	Absent	Coates ⁴⁷
Chickens					Weight gain	Not done	
NCS mice	Penicillin or terramycin	0.3 g/L water	Starting at 30-33 days of age for 1 week	15% gluten*	Weight loss	Terramycin: loss of Lactobacilli and Gram negative bacilli, increase in enterococci Penicillin 0.1 g: reduced Lactobacilli Penicillin 1 g: loss of lactobacilli and enterococci	Dubos ^{51, 88}
	Terramycin,	0.3 g/L		Pellets [‡]	Weight gain		
	Penicillin or terramycin	0.3 g/L		15% casein [§]	Weight loss		
	Penicillin	1 g/L			Weight loss		
	Penicillin	0.1 g/L			No change		
Ha/ICR mice	Penicillin or terramycin	0.3 g/L		Pellets [‡]	Weight gain		
				15% casein [§]	Weight gain		
ob/ob mice	Norofloxacin Ampicillin	1 g/L drinking water	17 days	Chow	Reduction in fat mass	Near elimination of aerobic bacteria, 3 log reduction in anaerobic bacteria	Membrez ⁶⁵
C57BL6 mice	Ampicillin & neomycin	1 g/L 0.5 g/L	4 weeks	HFD	Lower weight	lower <i>Bifidobacterium</i> , higher <i>Lactobacillus</i> , and <i>Bacteroides/Prevotella</i>	Cani ⁵²
ob/ob mice			4 weeks	Chow	Lower fat mass	lower <i>Bifidobacterium</i> , <i>Lactobacillus</i> , and <i>Bacteroides/Prevotella</i>	
Ob-CD14KO	none	NA	Lifelong	Chow	Lower fat mass	Not done	
Swiss mice	Ampicillin, neomycin, metronidazole	1 g/L	8 weeks	HFD	Less weight gain	Massive depletion of Bacteroidetes and Firmicutes, multi-log fold reduction in anaerobic and aerobic bacterial counts	Carvalho ⁶⁴
C57BL6 mice	Penicillin Vancomycin Chlortetracycline Pen. + Vanc.	1 mg/ kg body weight	3 weeks through life	Chow	Increased fat mass in all antibiotic groups	Increase in lachnospiraceae	Cho ⁴⁹
C57BL6 mice	Penicillin	1 mg/ kg body weight (0.007g/L drinking water)	Birth or 4 weeks, then lasting through life	Chow	greater increase in weight administered at birth, greater effect in males	No reduction in total microbial populations Consistently reduced <i>Lactobacillus</i> , <i>Allobaculum</i> , Rkenellaceae, and <i>Candidatus arthromitus</i> (SFB)	Cox ⁵⁰

Strain or species	Treatment	Dose	Timing	Diet	Effect on weight	Effect on microbiota	Reference
C57BL6 mice	Penicillin		Lifelong	HFD at 17 weeks	Pen promoted the diet-induced obesity and related metabolic effects		
C57BL6 mice	Penicillin		First 4 weeks, First 8 weeks, or lifelong	HFD at 6 weeks	Increased total, lean, and fat mass in all groups, greater effect in females		
GF-swiss webster rats	Pen-microbiota	NA	3 weeks of age	HFD	Increased fat and total mass in recipients of microbiota from antibiotic-treated mice	Lower <i>Lactobacillus</i> , <i>Allobaculum</i> , and Rkenellaceae	
C57BL6 mice	Vancomycin	2 mg/day	At weeks 12–20	HFD	Weight loss	Reduced <i>Clostridium</i> and <i>Bacteroides</i> , rise in enterobacteriaceae	Murphy ⁶⁶
Rats	Amoxicillin	150 mg/kg body weight	At 5–15 days old	Chow	No change in weight	Reduction in <i>Bacteroides</i> , <i>Lactobacillus</i> , and <i>Clostridium leptum</i> cluster at day 21 of life	Morel ⁶⁷

Abbreviations: HFD, high fat diet (45% calories from fat)

* gluten as a sole protein source (deficient in lysine and threonine)

[‡] complex mouse diet from Dietrich and Gambrill, Frederick, MD,

[§] casein as a sole protein source.