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The Gut–Liver Axis in the Control of Energy Metabolism and Food Intake in Animals

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Abstract

Recent research has convincingly demonstrated a bidirectional communication axis between the gut and liver that enables the gut microbiota to strongly affect animals' feeding behavior and energy metabolism. As such, the gut–liver axis enables the host to control and shape the gut microbiota and to protect the intestinal barrier. Gut microbiota–host communication is based on several gut-derived compounds, such as short-chain fatty acids, bile acids, methylamines, amino acid–derived metabolites, and microbial-associated molecular patterns, which act as communication signals, and multiple host receptors, which sense the signals, thereby stimulating signaling and metabolic pathways in all key tissues of energy metabolism and food intake regulation. Disturbance in the microbial ecosystem balance, or microbial dysbiosis, causes profound derangements in the regulation of appetite and satiety in the hypothalamic centers of the brain and in key metabolic pathways in peripheral tissues owing to intestinal barrier disruption and subsequent induction of hepatic and hypothalamic inflammation.

THE SIGNIFICANCE OF THE GUT–LIVER AXIS FOR COMMUNICATION BETWEEN THE MICROBIOTA AND THE ANIMAL

The term axis is increasingly used in the field of animal and human physiology to recognize a special association between two organs, even if these organs are anatomically wide apart and exert completely different functions, e.g., the liver–adipose tissue axis, gut–brain axis, and gut–liver axis. The term gut–liver axis was created to describe the association between two organs of the gastrointestinal tract, the gut and the liver. Apart from the fact that both organs have a common developmental origin from the ventral foregut endoderm, the term gut–liver axis primarily expresses that both organs directly communicate with each other via the biliary tract, the portal vein, and the systemic circulation. Because of the vascular connection between the intestine and liver through the portal vein, the liver receives approximately two-thirds of its blood from the intestine (1). Consequently, the liver is the first recipient of gut-derived products, such as dietary nutrients transported across the intestinal barrier, thereby acting as a key metabolic organ and a hub for the distribution of nutrients to other tissues.

The intestine harbors a great number of microbes, collectively called the microbiota, which utilize dietary and host-derived molecules (e.g., bile acids, endogenous protein), thereby producing various microbial metabolites [e.g., short-chain fatty acids (SCFA), methylamines, hydrogen sulfide, and phenolic and indolic compounds]. One critical structural component of the gut–liver axis is the intestinal barrier, which serves as a physical and functional barrier between the intestinal microbiota and the liver (2). Key elements of this barrier are the intestinal epithelial cells, which are tightly connected with adjacent cells by different tight junction proteins, as well as additional factors further strengthening the barrier, including mucins; antimicrobial peptides, such as lectins, defensins, and cathelicidins; immunoglobulins of type A (IgA); and commensal bacteria closely associated with the mucosa (3, 4). Commensal bacteria reinforce barrier integrity by stimulating cell-mediated immunity and producing protective metabolites (3). If the intestinal barrier is impaired, the liver is also confronted with microbial components, such as cell-wall components like lipopolysaccharide (LPS) and bacterial DNA, together referred to as microbial-associated molecular patterns (MAMP), and even intact microbes. In this case, the liver, i.e., hepatic immune cells such as Kupffer cells, hepatic stellate cells, natural killer (NK) cells, and NK T cells, exerts typical functions of an immune organ aiming to protect the other tissues from potentially harmful effects of these infectious stimuli (5).

In recent years, it has become increasingly clear from studies with germ-free versus conventionally raised animals and from animal studies in which the gut microbiota composition was altered by antibiotics or prebiotics that the gut microbiota profoundly affects the animals' feeding behavior and energy metabolism. This is most impressively shown by the observation that germ-free lean animals are resistant to diet-induced obesity and by the identification of an "obesogenic gut microbiota," whose metabolic phenotype is transmissible by transplantation of the gut microbiota from an obese animal into a germ-free lean animal (6–8). This dramatic impact of the gut microbiota on the animal's metabolism is explained by the ability of the gut microbiota to communicate with the host along the gut–liver axis via gut-derived compounds, which act as communication signals, and multiple host receptors, which sense the signals, thereby stimulating signaling and metabolic pathways in all key tissues of energy metabolism and food intake regulation. Importantly, although the term gut–liver axis implies that the liver is targeted by the gut in a unidirectional way, the communication between intestine and liver is bidirectional. This is reflected by the secretory function of the liver, namely, to produce bile acids, which together with other biliary components are secreted into the small intestine via the bile duct to facilitate

digestion of fat-soluble nutrients. Bile acids secreted into the intestine also modulate the gut microbiota composition, both directly by inhibiting the growth of specific bacterial groups and indirectly by stimulating the production of antimicrobial agents in the intestine (9). In addition, the liver along with the intestine is an important source of IgA antibodies, which are particularly important in the clearance of gut-derived antigens reaching the liver, thereby protecting the organism from pathogens. Indeed, transgenic mice lacking IgA exhibit an increased susceptibility to intestinal injury and intestinal barrier disruption (10). Liver-derived IgA is secreted from IgA-producing plasma cells that originate from the intestinal Peyer's patches and colonize hepatic portal regions and the biliary tract, from which IgA is transported into the bile (11). Thus, the host plays a key role in shaping the microbial communities in the intestine and in protecting the critical component of the gut–liver axis through the secretory functions of the liver.

REGULATION OF FOOD INTAKE AND ENERGY BALANCE IN THE BRAIN THROUGH INTEGRATING PERIPHERAL SIGNALS ABOUT THE ANIMAL'S NUTRITIONAL AND METABOLIC STATUS

Because of the vital role of regular intake of nutrients and energy for animals, regulation of food intake and energy homeostasis is a key function of the brain. Within the brain, distinct hypothalamic regions have been identified as being particularly important for regulating feeding behavior and energy homeostasis. Among these regions, the arcuatus nucleus (ARC), located in the mediobasal hypothalamus, plays a key role through sensing and integrating peripheral feedback signals about the animal's nutritional and metabolic status (12). To execute this role, the ARC contains two functionally antagonistic neuronal populations, which are targeted by the peripheral signals either directly after crossing the blood–brain barrier through specific receptors or indirectly via afferent vagus and sympathetic nerves. The anorexigenic neuronal population expresses either cocaine- and amphetamine-regulated transcript (CART) or pro-opiomelanocortin (POMC), both of which decrease appetite and, thus, energy intake by releasing different anorexigenic signals in the brain, such as α-melanocyte-stimulating hormone (αMSH) (13). In contrast, the orexigenic neuronal population increases appetite and, thus, energy intake through expressing the potent orexigens neuropeptide Y (NPY) and agouti-related peptide (AgRP), both of which inhibit the anorexigen-acting POMC-expressing neurons (14).

The peripheral signals comprise different peptide hormones secreted from specific endocrine cells in the intestine, called gut hormones (incretins), such as peptide YY, glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and ghrelin (15). Whereas peptide YY, GLP-1, and CCK are acute satiety-inducing signals secreted during the preabsorptive phase upon sensing of feed or specific nutrients (e.g., amino acids) by different receptors in the stomach and intestine and contribute to controlling meal size, the stomach-derived ghrelin is a powerful stimulator of appetite whose secretion is decreased in response to food intake (16). Important peripheral feedback signals acting during the postabsorptive phase, when systemic levels of nutrients (e.g., glucose) change, are released from the pancreas, such as insulin, glucagon, and pancreatic peptide. The anabolic hormone insulin suppresses appetite and food intake via several mechanisms, including insulin receptor–dependent induction of CART and αMSH and decreasing expression of the orexigens NPY and AgRP (17). Together with insulin, another peripheral feedback signal originating from white adipose tissues (WAT), leptin acts in the hypothalamus to reduce appetite and food intake (18). Because WAT is the main energy storage tissue and leptin reflects WAT size, leptin represents an important long-term feedback signal about the animal's energy storage capacity.

Because it senses these peripheral feedback signals in the hypothalamus, the animal is capable of tightly adapting nutrient and energy intake to the body's demand; e.g., during energy

restriction, when systemic levels of nutrients such as glucose decrease and leptin levels fall owing to reduction of WAT size, the orexigenic NPY- and AgRP- expressing neurons in the hypothalamic ARC are activated and stimulate the animal to consume food. Based on this, it is plausible that hypothalamic resistance to either of these peripheral signals severely impairs the adaptation of food intake to the animal's energy demand and disturbs energy homeostasis. Of note, the hormonal-induced adaptation to pregnancy is characterized by dramatic changes in food intake and energy balance, because of the increased demand of nutrients and energy for growth of fetal and maternal (reproductive and nonreproductive) tissues. In all pregnant mammals, food intake increases as a result of increased expression of orexigenic neuropeptides and stable or decreased expression of anorexigenic neuropeptides, leading to body weight gain due to increases of fetal and maternal tissues (WAT and reproductive tissues).

Owing to an increase in maternal fat mass, plasma leptin levels markedly increase in almost all animal species; e.g., they increase up to 25-fold in rodents (19, 20). However, despite this increase of leptin levels, the pregnancy-associated hyperphagia persists, which is explained by the development of physiological hypothalamic leptin resistance during this phase (21). Hypothalamic leptin resistance, which is mediated by pregnancy-associated hormonal changes, is an important maternal adaptation that counteracts the anorectic effect of leptin, thereby enabling the pregnant animal to cover its increased nutrient and energy demand. Interestingly, hypothalamic leptin resistance also occurs in many seasonal breeding species to adapt the animals to seasonal changes in energy supply and demand; e.g., seasonal leptin resistance allows animals to store energy when food supply is abundant to overcome subsequent periods of food shortage. For instance, sheep exhibit an increased appetite during the long-day season (spring, summer) when food is abundant, despite leptin levels being dramatically elevated during this phase compared with the short-day season (autumn, winter), in which sheep show normal leptin sensitivity and appetite adjusts in proportion to nutritional status (22, 23). A similar seasonal regulation of leptin sensitivity is also seen in certain rodent species, such as the Djungarian hamster (24). In addition, evidence exists that peripheral production of leptin in WAT also underlies a seasonal regulation. In lactating dairy cows, a long photoperiod (18 h) causes higher leptin expression in WAT than a short photoperiod (6 h) (25). This indicates that photoperiod-induced differences in peripheral production of leptin may also contribute to seasonal leptin sensitivity.

ROLE OF THE ENDOCANNABINOID SYSTEM IN REGULATING FOOD INTAKE AND ENERGY BALANCE IN ANIMALS

Within the last two decades, the endocannabinoid system (ECS) has emerged as a key signaling system evolved in animals as a mechanism to store energy through stimulating appetite and food intake and promoting fat accumulation (26). Although the ability to store energy has been an evolutionary advantage for free-living animals to cope with seasonal changes in food supply, it is probably a disadvantage when the individual has permanent access to food. In fact, although the central ECS is under negative control by the energy storage feedback signal leptin (27), convincing evidence shows that an overactive ECS promotes metabolic disorders, such as obesity, under conditions of unlimited availability of food (28, 29).

The ECS is composed of endogenous ligands called endocannabinoids (EC); enzymes synthesizing and degrading EC, such as N-acetyltransferase and fatty acid amide hydrolase (FAAH); and EC receptors mediating the effects of EC (30). The most prominent and best-characterized EC are anandamide (AEA) and 2-arachidonoylglycerol, both of which are produced on demand from membrane phospholipid-bound arachidonic acid, which serves as precursor. The two main receptors for EC are the cannabinoid receptors CB_1 and CB_2, which act as G protein–coupled

receptors. However, several other receptors are also activated or modulated by EC, such as peroxisome proliferator–activated receptors and different transient receptor potential vanilloid 1 isoforms, indicating that EC can exert their biological effects via multiple signaling pathways. The ECS is found in many tissues but appears to play a particular role in tissues involved in the regulation of food intake and energy balance, such as the brain, but also in key metabolic tissues such as liver, intestine, skeletal muscle, and WAT (31). In the above-mentioned tissues, CB_1 is widely expressed, whereas CB_2 is found primarily in immune and blood cells (32). Initial knowledge about ECS function has been gained from the observation that exogenous cannabinoids from the marijuana plant *Cannabis sativa* stimulate appetite and intake of food, in particular highly palatable food (sweets, fat-rich food), in animals and humans (33).

The orexigenic effect of cannabinoids has long been attributed solely to activation of CB_1-dependent signaling pathways in the above-explained hypothalamic neuronal subpopulations involved in the regulation of food intake and energy status, because pharmacological blockade of CB_1 by the blood–brain barrier–penetrating CB_1 antagonist rimonabant—the first clinically approved CB_1 antagonist—reduced food intake and body weight in rodents and humans (34–36). However, peripherally restricted CB_1 antagonists, which were developed upon withdrawal of approval of rimonabant owing to severe adverse side effects (depression, anxiety), were also found to effectively reduce food intake and to successfully treat diet-induced obesity (37). This clearly indicates that CB_1-dependent signaling in peripheral tissues along the gut–liver axis is also involved in the regulation of food intake and energy metabolism.

Despite most of the knowledge about ECS function and regulation being gained from studies in laboratory animals, such as mice and rats, few studies demonstrate that the ECS is also important in regulating energy homeostasis in livestock animals. In line with its orexigenic action, in beef cattle the plasma concentration of the EC AEA increases throughout the finishing period, and the more efficient animals (with greater gain-to-feed ratio) have a greater AEA plasma concentration, suggesting that plasma EC are useful predictors of growth and feed efficiency (38, 39). In dairy cows, alterations in the peripheral ECS (WAT, liver) were reported in the periparturient period (40, 41). Although an upregulation of hepatic FAAH soon after parturition has been interpreted as a mechanism to prevent excessive EC production in the liver of cows postpartum (40), EC levels in WAT were higher in postpartum than in prepartum dairy cows (41). Although the exact relevance of these alterations in peripheral ECS in postpartum dairy cows is unclear, these alterations likely reflect or even contribute to the metabolic adaptations to lactation. In addition, Zachut et al. (41) revealed that activation of WAT ECS is higher in dairy cows exhibiting marked weight loss, lipolysis, and signs of WAT inflammation than in cows with low weight loss, suggesting that increased ECS stimulation in these cows may be related to elevated lipolysis levels and WAT inflammation.

MICROBIOTA REGULATION OF FOOD INTAKE AND ENERGY METABOLISM VIA THE GUT–LIVER AXIS

Regulation Through Modulating the Intestinal Endocannabinoid System

A pioneering study from Muccioli et al. (42) provided strong evidence for gut microbiota regulation of the ECS. This study demonstrated that the intestinal microbiota regulates the peripheral ECS in the intestine and that obesity-induced dysregulation of intestinal ECS causes a disruption of the intestinal barrier. This was deduced from the finding that increased activity of the intestinal ECS (elevated intestinal levels of AEA and CB_1 mRNA) in diet-induced obese mice was associated with elevated plasma levels of LPS, which is indicative of an impairment of intestinal barrier. Accordingly, treatment of lean mice with a CB_1 agonist mimicked obesity-induced activation of the

ECS and elevated plasma levels of LPS. In contrast, modulating the gut microbiota by feeding a prebiotic or more drastically by an antibiotic (but also pharmacological blockade of intestinal CB_1 receptor) in obese mice resulted in improved intestinal barrier function and decreased activity of intestinal ECS (42). Similar to the intestine, the ECS tone in WAT of the obese mice was increased, as evidenced by elevated CB_1 expression and AEA levels in WAT, whereas the ECS activity of WAT of the obese mice was reduced by feeding the prebiotic (42). Several lines of evidence exist that an overactive ECS in WAT promotes obesity. For instance, CB_1 expression is higher in mature adipocytes than in preadipocytes, and activation of CB_1 in preadipocytes promotes their differentiation into mature adipocytes (43). In addition, activation of CB_1 in adipocytes stimulates lipogenesis and fat accumulation and inhibits mitochondrial biogenesis (44, 45), whereas the opposite is the case when CB_1 receptor is pharmacologically blocked or genetically deleted in adipocytes (46, 47). In agreement with this, selective CB_1 knockout in mature adipocytes was sufficient to protect mice from diet-induced obesity (48). Moreover, blockade of CB_1 receptor in diet-induced obese mice was associated with reduced macrophage retention in WAT and decreased local and systemic inflammation (49), indicating that inhibition of peripheral CB_1 receptors reduces the systemic low-grade inflammatory state associated with obesity. Additionally, this study demonstrated that the anti-obesity effect of CB_1 receptor blockade was associated with a significant alteration in gut microbiota composition, with an increase in *Akkermansia muciniphila* and a decrease in the families Lachnospiraceae and Erysipelotrichaceae (49).

According to the findings from Muccioli et al. (42), the intestinal barrier as a key component of the gut–liver axis plays a critical role in the obesogenic effect of ECS activation in WAT, because LPS, which is systemically elevated as a consequence of an impaired intestinal barrier, stimulates production of EC ligands, particularly AEA, in white adipocytes and/or WAT macrophages (50, 51). Activation of ECS in response to an increased intestinal permeability leading to systemically elevated levels of LPS may also promote metabolic disorders in other peripheral tissues, such as liver and skeletal muscle. Similar to WAT, activation of CB_1 in the liver promotes lipogenesis, thereby inducing fat accumulation and ultimately hepatic steatosis (29, 52). In line with this, mice with a hepatocyte-specific CB_1 receptor deficiency do not develop fatty liver in response to a high-fat diet (29). Interestingly, studies in animal models of obesity demonstrate that the ECB system is affected even in skeletal muscle; according to these studies, increased activity of the ECB system in skeletal muscle causes an impairment of oxidative metabolism and reduced mitochondrial biogenesis (45). Overall, these findings clearly show that activation of the ECS in peripheral tissues leading to a dysregulation of energy metabolism in key metabolic organs occurs as a consequence of an impairment of a key structural component of the gut–liver axis: the intestinal barrier. Dietary strategies aiming to maintain intestinal barrier integrity are therefore of high relevance with regard to protection from metabolic disorders induced by ECS activation.

It has been recognized in recent years that postpartum dairy cows typically develop a chronic low-grade inflammatory condition (53) as a result of infectious diseases (mastitis, endometritis) but also intestinal disorders associated with increased intestinal permeability (subacute rumen acidosis, abomasal displacement) (54, 55), which increases systemic levels of LPS and other inflammatory stimuli. These stimuli are considered as driving forces in the development of typical postpartum disorders of energy and lipid metabolism in the liver, such as fatty liver. This view is based on the observation that these stimuli can activate stress-signaling pathways, such as endoplasmic reticulum (ER) stress, which itself is known to stimulate de novo synthesis of fatty acids in the liver (56). Regarding the link between increased intestinal permeability, activation of ECS in peripheral tissues (liver, WAT), and stimulation of de novo synthesis of fatty acids by ECS activation and the recent observation that the peripheral ECS is activated in postpartum versus prepartum dairy cows (41), fatty liver development in the liver of postpartum dairy cows

may involve both activation of hepatic stress-signaling pathways and hepatic ECS activation. In line with this view, it was recently shown that fatty acid–induced ER stress promotes lipid accumulation in calf hepatocytes and that ER stress exists in the liver of severe fatty liver cows (57).

Regulation Through Gut Microbiota–Derived Signals

As described above, the gut microbiota profoundly affects animals' energy metabolism and food intake (6–8), because the gut microbiota communicates with the host along the gut–liver axis through various microbiota-derived bioactive compounds, which initiate signaling through receptors in different tissues of the host (**Figure 1**). Several of these microbiota-derived bioactive compounds, such as SCFA, bile acids, methylamines, amino acid–derived metabolites, and MAMP, and their signaling mechanisms underlying the regulation of the host's energy metabolism and food intake are discussed below.

Role of Short-Chain Fatty Acids

The quantitatively most-important bacterial metabolites are SCFA, which are produced during fermentation of indigestible carbohydrates (resistant starch, inulin, cellulose) in the gut (caecum and colon). The most prominent SCFA are acetate, propionate, and butyrate, but several other SCFA, such as valerate, isovalerate, formate, and caproate, are also formed during bacterial fermentation, although at lower levels (<5% of total SCFA). SCFA are efficiently absorbed at high rates (90–95%) from the intestine (58) and partially metabolized within the intestinal epithelial cells, thereby exerting trophic effects on the epithelial mucosa (59). SCFA not used by intestinal cells are transported via the portal vein to the liver, where they can be used as substrates for gluconeogenesis (propionate) and lipogenesis (acetate, butyrate). SCFA are also substantially available in the systemic circulation and found in humans at concentrations of 19–160 μM (acetate), 1–13 μM (propionate), and 1–12 μM (butyrate) (60), depending mainly on the dietary amount of indigestible carbohydrates. In recent years, different SCFA receptors, such as free fatty acid receptor FFAR2 (also known as GPR43), FFAR3 (also known as GPR41), and even the hydrocarboxylic acid receptor GPR109A (also known as niacin receptor) (61, 62), have been discovered in the nervous system and in many metabolic tissues, including liver, WAT, and skeletal muscle. This indicates that gut-derived SCFA also act as important signaling molecules used for communication between the microbiota and host tissues via the gut–liver axis, and thereby affect host metabolism (**Figure 2**). This is underscored by recent observations that the expression of SCFA receptors in key metabolic tissues like WAT and liver in livestock animals, such as dairy cows, changes during the periparturient period, likely as a mechanism to adapt to the animal's changing energy demand during this period (63–65).

Several lines of evidence have suggested in recent years that systemic availability of SCFA via the gut–liver axis plays an important role in the regulation of food intake through inducing satiety. Xiong et al. (66) provided evidence in this regard, showing that SCFA stimulate secretion of satiety-inducing leptin in both a mouse adipocyte cell line and mouse adipose tissue in primary culture in a GPR41-dependent manner. In addition, this study revealed that acute oral administration of propionate increases circulating leptin levels in mice (66). Likewise, incubation with SCFA stimulates leptin secretion from bovine adipocytes (67), and oral and intravenous administration of propionate increases leptin gene expression in WAT of sheep (68). Also, oral administration of a mix of SCFA caused an increase in plasma concentration of leptin in pigs (69). In addition, Frost et al. (70) demonstrated that acetate administered into the colon of mice crosses

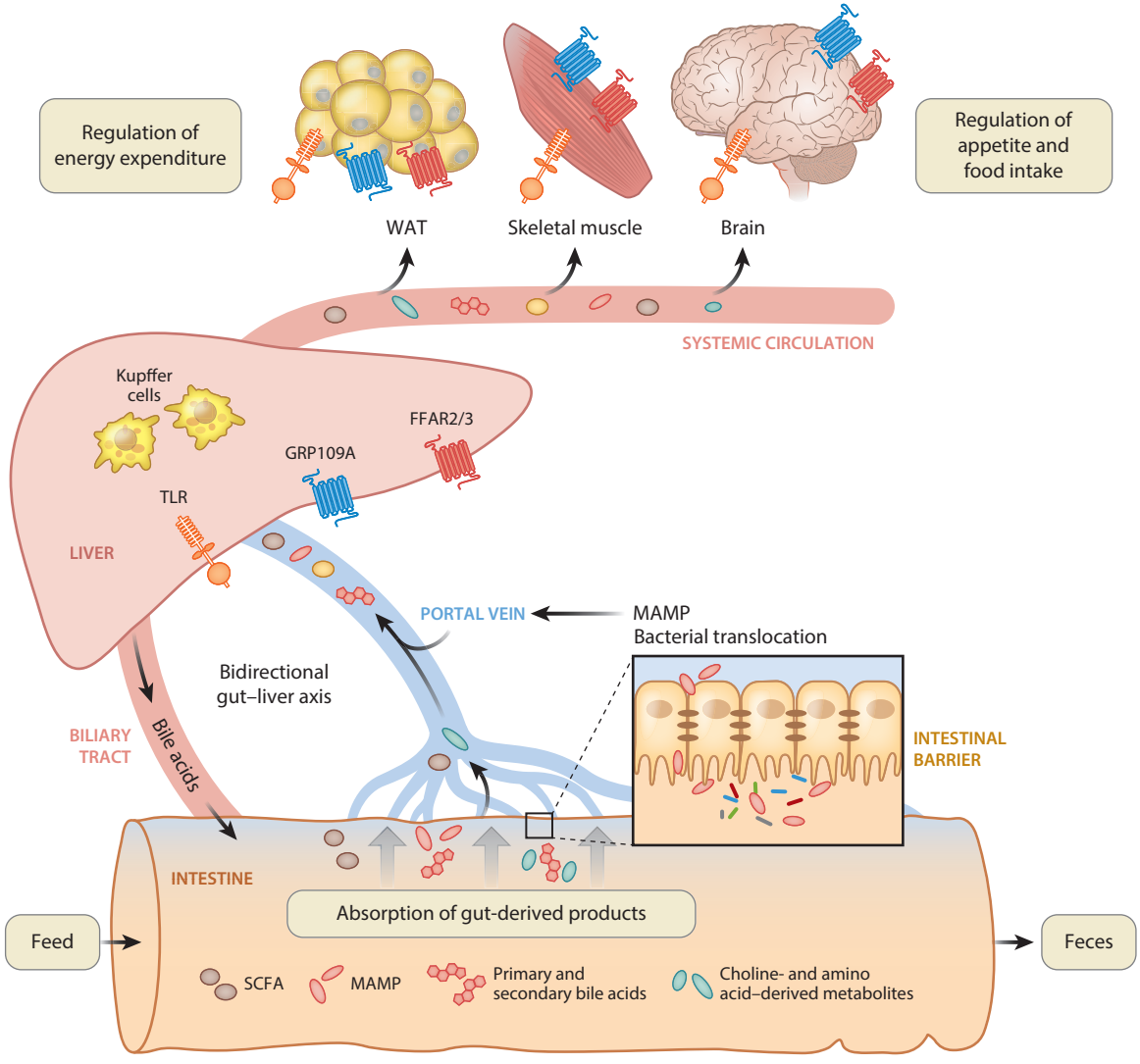


Figure 1

The gut–liver axis is a bidirectional communication axis enabling the gut microbiota to strongly affect the animals' feeding behavior and energy metabolism and enabling the host to control and shape the gut microbiota and protect the intestinal barrier. Gut microbiota–host communication is based on several gut-derived compounds, such as short-chain fatty acids (SCFA), bile acids, methylamines, amino acid–derived metabolites, and microbial-associated molecular patterns (MAMP), which act as communication signals, and multiple host receptors, such as Toll-like receptors (TLR), free fatty acid receptors (FFAR2/3, GPR109A), receptors for bile acids, and many others, which sense the signals, thereby stimulating signaling and metabolic pathways in all key tissues of energy metabolism, such as liver, skeletal muscle, and white adipose tissue (WAT), and food intake regulation (brain). Increased translocation of MAMP as a consequence of intestinal barrier disruption causes profound derangements in the regulation of appetite and satiety in the brain and in key metabolic pathways in peripheral tissues owing to induction of hepatic and hypothalamic inflammation.

the blood–brain barrier and is taken up by the brain, and that intraperitoneal injection of acetate decreases food intake by changing the hypothalamic expression of orexigenic/anorexigenic neuropeptides in a way that causes appetite suppression. Uptake of acetate into the brain has been shown in humans as well (71), indicating that direct regulation of appetite by SCFA likely also

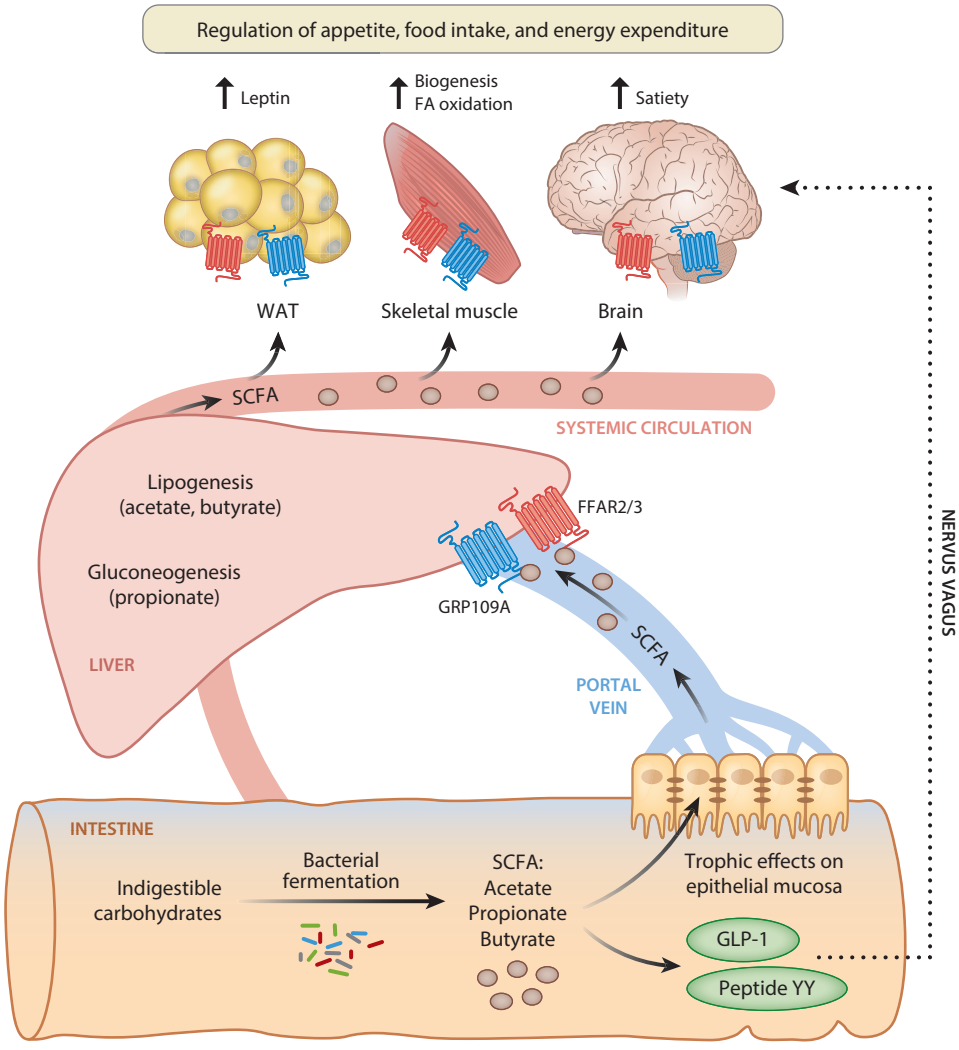


Figure 2

Short-chain fatty acids (SCFA), such as acetate, propionate, and butyrate, are the quantitatively most-important gut-derived products produced during bacterial fermentation of indigestible carbohydrates in the intestine. SCFA are efficiently absorbed at high rates (90–95%) from the intestine and partially metabolized within the intestinal epithelial cells, thereby exerting trophic effects on the epithelial mucosa. SCFA not used by intestinal cells are transported to the liver via the portal vein, where they can be used as substrates for gluconeogenesis (propionate) and lipogenesis (acetate, butyrate). In addition, gut-derived SCFA also act as important signaling molecules for communication between the microbiota and host tissues, such as liver, skeletal muscle, white adipose tissue (WAT), and brain, thereby regulating appetite, food intake, and energy expenditure by activating various receptors for SCFA, such as free fatty acid receptors (FFAR2, FFAR3) and hydrocarboxylic acid receptor (GPR109A). In addition, butyrate and to a lesser extent propionate, but not acetate, stimulate the secretion of the gut hormones peptide YY and glucagon-like peptide-1 (GLP-1), both of which induce satiety in the brain by suppressing orexigenic neurons.

occurs in humans. Although not within the primary scope of this review, it should be pointed out that SCFA also regulate appetite and food intake, and thus energy balance, independent of the gut–liver axis. Studies in rats and pigs showed that intracolonic and ileal infusion, respectively, of a mixture of SCFA increases secretion of the gut hormone peptide YY (72, 73), which is known to induce satiety in the brain. A recent study aimed at determining the individual contribution of SCFA on gut hormone secretion demonstrated that butyrate and to a lesser extent propionate, but not acetate, stimulate the secretion of peptide YY and GLP-1 (74). In addition, several studies reported that feeding fermentable carbohydrates increases expression and secretion of peptide YY and GLP-1 in rodents (75, 76), both of which induce satiety in the brain by suppressing NPY and activating POMC neurons in the hypothalamic ARC.

Apart from satiety-inducing effects of SCFA, convincing evidence exists that systemic SCFA influences energy balance by exerting direct effects in key metabolic tissues, such as WAT, skeletal muscle, and liver. Gao et al. (77) demonstrated that dietary administration of butyrate prevents obesity development in mice through enhancing energy expenditure by increasing mitochondrial function and biogenesis and fatty acid oxidation in skeletal muscle and brown adipose tissue. Increased mitochondrial fatty acid oxidation in the skeletal muscle of these mice was probably the result of a butyrate-induced increase of the proportion of type I muscle fibers, which are rich in mitochondria and have high oxidative capacity. Similarly, propionate also enhanced energy expenditure through increasing sympathetic nervous system activity (78). An enhancement of sympathetic function increases heart rate and diet-induced thermogenesis (79). Kimura et al. (78) demonstrated in a series of in vitro and in vivo studies with wild-type and GPR41 knockout mice that activation of sympathetic ganglion neurons by propionate is mediated by a GPR41-dependent mechanism. Also, injection of acetate into rats increased expression of fatty acid oxidation in brown adipose tissue, indicating a stimulation of energy expenditure (80).

Besides stimulating energy expenditure, systemic SCFA improve metabolic health through enhancing WAT lipid buffering capacity by inhibiting intracellular lipolysis. The antilipolytic effect of SCFA is thought to reduce ectopic fat accumulation and to improve insulin sensitivity by decreasing lipid overflow into the circulation (81). The antilipolytic role has been ascribed particularly to acetate, which was reported 50 years ago to decrease plasma free fatty acids after a single oral acetate ingestion (82). Moreover, elevation of circulating acetate concentration owing to acute colonic administration of three physiologically relevant mixtures of SCFA was found to reduce circulating glycerol concentration in overweight males, indicating a reduced whole-body lipolysis (83). Recently, the same group showed that physiologically relevant levels of acetate exert an antilipolytic response, via FFAR2- and FFAR3-mediated attenuation of HSL phosphorylation (at Ser650), in a human white adipocyte model (84). Because the niacin receptor GPR109A, which is responsible for mediating the antilipolytic effects of nicotinic acid in WAT (85), is activated by butyrate (62), the antilipolytic effect of butyrate might also involve GPR109A.

Lastly, beneficial metabolic effects of SCFA indicative of a reduction of ectopic fat accumulation were also observed in the liver. In pigs, oral infusion of a mix of acetate, propionate, and butyrate caused a decreased expression of lipogenic genes, an increased expression of fatty acid oxidation genes, and a reduction of total fat content in liver (69). These effects might be directly caused by systemic SCFA reaching the liver, because hepatocytes are known to express different receptors for SCFA, such as GPR41 and GPR43 (61). However, effects of SCFA in the liver might be also secondary to an improvement of intestinal barrier function. Several studies demonstrated that SCFA improve critical components of the intestinal barrier, such as the expression of tight junction proteins and mucin glycoproteins (86). As a consequence, the intestinal permeability for bacterial components such as LPS is reduced, thereby decreasing the exposition of the liver to LPS via the portal vein. It is discussed elsewhere in this article that LPS is sensed by different receptors,

such as Toll-like receptors (TLR) on Kupffer cells and hepatic stellate cells (87). TLR signaling activates inflammatory and stress-signaling pathways, such as nuclear factor-kappa B (NF-κB) and ER stress-induced unfolded protein response (UPR), which promotes hepatic inflammation and hepatic fat accumulation owing to stimulating de novo lipogenesis.

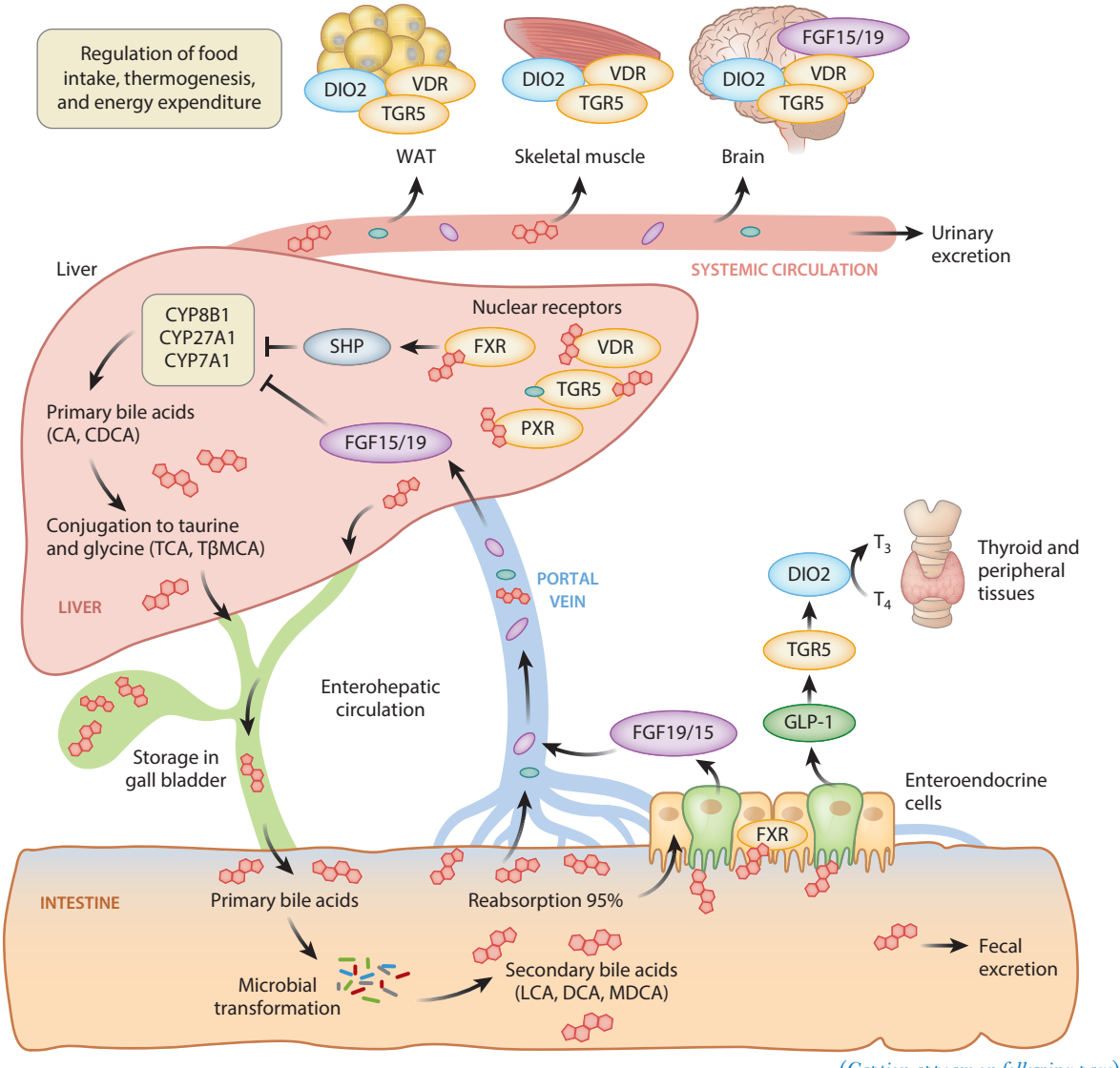
Role of Bile Acids

Bile acids [cholic acid (CA) and chenodeoxycholic acid (CDCA) in humans and additionally α- and β-muricholic acid (MCA) in rodents] are enzymatically synthesized from cholesterol in the liver via the classical (neutral) pathway, which accounts for more than 75% of bile acid synthesis, and the alternative (acidic) pathway. Subsequently, these primary bile acids are conjugated within the hepatocyte to glycine (predominantly in humans) or taurine (predominantly in rodents), leading to glycine- and taurine-conjugated bile acids. The glycine and taurine conjugates are subsequently released into the duodenum, where they facilitate digestion of fat-soluble food components owing to their detergent properties. The vast majority (>95%) of these bile acids are reabsorbed from the ileum and transported back via the portal vein to the liver, where they are secreted back to the biliary tract in a process called enterohepatic circulation. Although most bile acids are taken up from the portal vein into the liver via different bile acid transporters (88), a certain fraction of bile acids becomes available in the systemic circulation by bypassing their uptake out of liver sinusoids (89). Because of the high bile acid flux in the portal vein following food digestion, systemic levels of bile acids increase up to 15 μM in the postprandial phase, compared with less than 5 μM in the fasting state (90). The small amount (<5%) of glycine and taurine conjugates escaping the enterohepatic recycling process is metabolized by the gut microbiota. After initial deconjugation by microbial bile salt hydrolase, which is important for protection of bacteria against bile acid toxicity (91), the deconjugated bile acids are further metabolized (dehydrogenation and dihydroxylation), thereby leading to the secondary bile acids [mainly deoxycholic acid (DCA) and lithocholic acid (LCA) in humans and additionally murideoxycholic acid in rodents and, less prominently, hyodeoxycholic acid and ursodeoxycholic acid (UDCA)].

In the last two decades, it has become clear that bile acids are not only simple detergents but also potent signaling molecules exhibiting important regulatory effects on metabolic and signaling pathways, at both the intestinal and the systemic level, through binding to different nuclear hormone receptors, including farnesoid X receptor (FXR) (92), pregnane X receptor (93), vitamin D receptor (94), and Takeda G protein–coupled receptor 5 (TGR5) (95) (**Figure 3**). Because the potency of bile acids to activate bile acid receptors varies among different primary and secondary bile acids, as shown for FXR (CDCA > CA > DCA > LCA), and because the composition of the intestinal and circulating bile acid pool is greatly affected by the gut microbiota, it is obvious that changes of the gut microbiota can significantly affect host metabolism and health. Interestingly, certain bile acids, such as UDCA, which is found in humans, and the murine Tauro-βMCA, exhibit antagonistic activities on FXR (96). Convincing evidence has been discovered recently that the bile acid–sensing receptor FXR represents a crucial link between the gut microbiota and host energy metabolism. FXR-dependent mechanisms play an important role in regulating bile acid homeostasis through feedback inhibition of hepatic CYP7A1 (97), the rate-limiting enzyme in the classical pathway of bile acid synthesis, but also of other bile acid synthesis genes, such as CYP8B1 and CYP27A1 (98).

Feedback inhibition of bile acid synthesis is mediated by activation of hepatic FXR, which induces small heterodimer partner (SHP), thereby repressing bile acid synthesis genes. In addition, activation of intestinal FXR by bile acids also causes negative inhibition of bile acid synthesis owing to induction of the enterokine fibroblast growth factor (FGF) 19 in human and FGF15

in mouse, which reach the liver via the portal vein and downregulate hepatic CYP7A1 via activation of FGFR4 signaling (9). Interestingly, activation of intestinal FXR is also closely linked with metabolic diseases, such as obesity and hepatic steatosis (99, 100). This is evident from the observation that intestine-specific FXR-deficient mice are protected against diet-induced obesity and steatosis (99, 100). In addition, inhibition of intestinal FXR signaling by modulation of the mouse gut microbiota using an antibiotic mixture or the antioxidant tempol was also found to decrease obesity and hepatic steatosis (99, 100), which has been attributed to changes in the intestinal bile acid spectrum owing to the altered gut microbiota. Indeed, in germ-free mice, which lack a gut microbiota capable of deconjugating, dehydrogenating, and dehydroxylating bile acids, the bile acid profile in the distal small intestine and caecum almost exclusively contains Tauro-βMCA and Tauro-CA (101). In contrast, the intestinal bile acid spectrum of conventionally raised



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Primary bile acids are synthesized from the liver and conjugated within the hepatocyte, leading to glycine- and taurine-conjugated bile acids. The vast majority (>95%) of these bile acids are reabsorbed from the ileum and transported back via the portal vein to the liver. Although most bile acids are taken up from the portal vein into the liver via different bile acid transporters, a certain fraction of bile acids becomes available in the systemic circulation by bypassing their uptake out of liver sinusoids. The small amount (<5%) of glycine and taurine conjugates escaping the enterohepatic recycling process are metabolized by the gut microbiota, leading to the secondary bile acids (mainly DCA, LCA, and MDCA). In addition, bile acids act as potent signaling molecules, exhibiting important regulatory effects on metabolic and signaling pathways at both the intestinal and systemic level by binding to different nuclear hormone receptors, including FXR, pregnane X receptor and vitamin D receptor, and TGR5 in all key tissues of energy metabolism, such as liver, skeletal muscle, and WAT, and of food intake regulation (brain). FXR is a crucial link between gut microbiota and host energy metabolism. FXR-dependent mechanisms play an important role in regulating bile acid homeostasis through feedback inhibition of hepatic CYP7A1, the rate-limiting enzyme in the classical pathway of bile acid synthesis, but also of other bile acid synthesis genes, such as CYP8B1 and CYP27A1. Feedback inhibition of bile acid synthesis is mediated by activation of hepatic FXR, which induces SHP, thereby causing repression of bile acid synthesis genes. In addition, activation of intestinal FXR by bile acids also causes negative inhibition of bile acid synthesis owing to induction of the enterokine FGF19 in human or FGF15 in mouse, which reaches the liver via the portal vein and downregulates hepatic CYP7A1 via activation of FGFR4 signaling. FGF19/15 can also pass the blood–brain barrier and bind to a hypothalamic FGF19/FGF15 receptor, which decreases orexigenic neuronal activity, thereby decreasing appetite and food intake. Through activating TGR5, bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. This effect is mediated by TGR5-dependent activation of DIO2, which converts the inactive thyroxine into the active triiodothyronine, thereby resulting in enhanced energy expenditure in brown adipose tissue and skeletal muscle. Abbreviations: CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; DIO2, type 2 iodothyronine deiodinase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; LCA, lithocholic acid; MDCA, murideoxycholic acid; PXR, pregnane X receptor; SHP, small heterodimer partner; TβMCA, tauro-β-muricholic acid; TCA, tauro-cholic acid; TGR5, Takeda G-protein-coupled receptor 5; VDR, vitamin D receptor; WAT, white adipose tissue.

mice exhibits greater diversity, with high levels of CA and low levels of Tauro-βMCA, both of which indicate efficient deconjugation by the gut microbiota (101). Owing to the strong structure dependence of bile acids to activate FXR (CA is a potent FXR activator, whereas Tauro-βMCA even acts as an FXR antagonist), extensive microbial metabolism of Tauro-βMCA results in increased intestinal FXR activity in conventionally raised mice, whereas decreased metabolism of Tauro-βMCA suppresses intestinal FXR activity in germ-free mice (101).

Although these studies convincingly show that inhibition of FXR signaling reduces obesity and liver steatosis in mice, the precise mechanisms by which FXR regulates host metabolism are unclear. According to a recent study, increased intestinal FXR signaling may contribute to obesity by shifting the gut microbiota to a more obesogenic configuration; this study (102) demonstrated that the serum bile acid profile of intestine-specific FXR-deficient mice is clearly different from that of wild-type mice. The gut microbiota of FXR-deficient mice exhibited a phylum-wide increase in Bacteroidetes and phylum-wide reduction of Firmicutes, both of which have been associated with protection from obesity (103). In addition, Parséus et al. (102) showed that transfer of the microbiota from diet-induced obese FXR-deficient mice to germ-free wild-type mice resulted in less fat mass gain. Gut microbiota alterations are likely the result of increased production of bile acids, which can modulate bacterial growth and microbial ecology in the gut (104) by, for instance, stimulating the production of antimicrobial agents such as angogenin-1 and RNase family member 4 in the small intestine in a FXR-dependent manner (102, 105). Regulation of host metabolism via activation of intestinal FXR might also involve the above-mentioned enterokine FGF19 (in human)/FGF15 (in mouse), which can pass the blood–brain barrier and bind to a hypothalamic FGF19/FGF15 receptor (106). Of note, intracerebroventricular administration of FGF19 in mice decreases orexigenic AgRP/NPY neuronal activity (107). Because the brain abundantly expresses FXR (108), it is also interesting in this context that circulating bile acids, at least the unconjugated bile acids CA, CDCA, and DCA, can even cross the blood–brain barrier (109). Thus, direct actions of bile acids in the regulation of food intake and energy balance in the brain cannot be ruled out.

Apart from FXR and other nuclear hormone receptors, TGR5 signaling induces relevant effects with regard to regulation of energy metabolism through bile acids via the gut–liver axis. For instance, activation of TGR5 by bile acids was reported to induce energy expenditure by promoting intracellular thyroid hormone activation (110). This effect was mediated by TGR5-dependent activation of type 2 iodothyronine deiodinase, which converts the inactive thyroxine into the active triiodothyronine, thereby resulting in increased BAT activity and enhanced energy expenditure in murine BAT and human skeletal muscle (110). In line with this, Broeders et al. (111) found that oral supplementation with the bile acid CDCA increased the thermogenic activity of primary adipocytes derived from the human brown adipose tissue in the neck region but not in adipocytes from WAT. Apart from regulation via the gut–liver axis, bile acids can regulate food intake via TGR5-dependent secretion of GLP-1 from enteroendocrine L cells (112).

Role of Choline Metabolites

Recent research indicates that gut microbiota–derived choline metabolites, such as trimethylamine (TMA), contribute to severe disturbances of hepatic lipid metabolism and even promote cardiometabolic disorders, such as atherosclerosis. Among the commensal gut bacteria in the mammalian intestine, several families from the Firmicutes and Proteobacteria phyla have been identified as potential TMA producers (113). Gut microbiota–dependently produced TMA reaches the liver via the portal circulation, where it is subsequently oxidized by hepatic flavin-containing monooxygenases forming TMA-*N*-oxide (TMAO). Via the same gut microbiota–host cometabolic pathway, carnitine (3-hydroxy-4-*N*,*N*,*N*-trimethylaminobutyric acid) was also reported to increase circulating levels of TMAO (114). TMAO has recently attracted great medical attention because it was found to directly promote atherosclerosis in mice (115), and increased TMAO levels are associated with an increased risk of major adverse cardiovascular events (116). Apart from this, TMAO was found to promote the development of fatty liver in mice fed a high-fat diet (117). In line with this, a positive correlation between the circulating TMAO level and the presence and severity of nonalcoholic fatty liver was recently found in Chinese adults (118). The increased risk for the development of fatty liver disease in response to TMAO has been attributed to the lowering of the total bile acid pool by inhibiting key enzymes of bile acid synthesis and limiting the enterohepatic circulation of bile acids (114). As a consequence of this, bile acid–induced signaling pathways such as FXR in the intestine and liver are modulated, thereby disturbing lipid and energy metabolism. In addition, elevated systemic TMAO levels are also concomitant with decreased levels of host-produced phosphatidylcholine, which promotes hepatic steatosis because phosphatidylcholine is required for hepatic excretion of lipids via very-low-density lipoprotein particles.

Role of Amino Acid–Derived Metabolites

Apart from indigestible carbohydrates reaching the caecum and colon, proteins escaping digestion in the small intestine are used by the gut microbiota for fermentation. Fermentation of amino acids from undigested/partially digested proteins produces a wide array of different compounds, including branched-chain fatty acids, ammonia, hydrogen sulfide, and phenolic and indolic compounds, as well as amines and polyamines (119). Despite certain metabolites like hydrogen sulfide being detrimental for the colonic epithelium at high concentrations because they induce a proinflammatory response (120), metabolites derived from aromatic amino acid metabolism, such as indole and its microbiota–host cometabolites (bacterial products modified by host enzymes), indole-3-aldehyde or indole-3-lactate, were found to improve gut barrier function and reduce intestinal inflammation (121, 122), thereby likely protecting from metabolic endotoxemia. The

stimulatory effect of endotoxins such as LPS on lipogenesis in peripheral tissues is explained above. Apart from local effects in the intestine, indole crosses the intestinal barrier and reaches the liver via the portal vein. Of note, Beaumont et al. (123) recently demonstrated that indole reduces hepatic inflammation induced by LPS in an ex vivo model using cut liver slices. Using the same model, the authors also demonstrated that indole decreases hepatic inflammation in obese mice that is characterized by metabolic endotoxemia and liver inflammation (123). Based on their results, the authors proposed administering indole-producing bacteria as probiotics to increase indole availability in the liver.

Role of Microbial Components

Microbial components such as LPS, peptidoglycan, lipoteichoic acid, flagellin, and bacterial nucleic acids (DNA, RNA), collectively termed MAMP, are present at low levels in the liver and systemic circulation even in healthy animals. This indicates that the intestinal barrier does not completely prevent the translocation of microbial components into the portal circulation and that the liver is constantly exposed to microbial components. However, because the liver does not display overt signs of inflammation under these conditions (124), it can be assumed that physiological levels of MAMP are not detrimental to animal health. Interestingly, low levels of MAMP may even be important for animals to initiate an effective adaptive immune response in the case that the liver is acutely exposed to high levels of MAMP, and for developing lasting immunity against certain pathogens (125). In addition, owing to the ability of Kupffer cells, which are liver-resident macrophages, to capture and/or kill whole bacteria and MAMP (126), the liver acts like a second firewall after the intestine (5). Besides Kupffer cells, several other cell types are important cellular constituents of this second firewall, such as intrahepatic mucosal-associated invariant T cells, which are predominantly located around the intrahepatic bile ducts in the vicinity of the portal tract; intrahepatic Tregs; dendritic cells; and NK cells (127). Owing to this innate defense system, the liver largely prevents the translocation of MAMP into the systemic circulation, thereby protecting other tissues from infectious and inflammatory stimuli and maintaining animal health. However, if the intestinal barrier is disrupted ("leaky gut"), exposure of the liver to whole bacteria and MAMP is dramatically increased, which can overcharge the protective mechanisms of the liver, thereby promoting disease development. Strong evidence has been found in recent years that an elevation of systemic MAMP levels owing to loss of intestinal barrier integrity causes a dysregulation of food intake and energy metabolism, a state that has been named metabolic endotoxemia (128). In very simplified terms, hepatic and hypothalamic inflammation induced by the disruption of intestinal barrier integrity are the two key events underlying this dysregulation of food intake and energy metabolism.

Induction of Hepatic and Hypothalamic Inflammation by Microbial Components

In the liver, MAMP such as LPS are recognized by specific pattern recognition receptors (PRR), which are abundantly expressed in the above-mentioned hepatic immune cells but also in hepatic parenchymal cells and have been evolved to sense and respond to microbial stimuli by triggering an acute immune response. One important class of PRR are the TLR, mammalian homologs to the *Drosophila* Toll gene, which encodes a receptor for host defense against microbial infections. Upon sensing MAMP, TLR activate different downstream signaling adaptor proteins, including myeloid differentiation primary response 88, interleukin-1 receptor-associated kinases, and TRAF6, which trigger various inflammatory and stress-signaling pathways, such as NF-κB, c-JUN N-terminal kinase (JNK), and ER stress-induced UPR (129). Apart from TLR, the large

family of nucleotide-binding oligomerization–like receptors (NLR), which consists of several subfamilies that share a common MAMP-sensing domain but differ in their N-terminal effector domains, has also been identified to promote the development of hepatic and systemic inflammation in response to MAMP. Among the NLR, the NLRP subfamily is best known for its role in inducing the formation of a multi-protein inflammatory complex, called the inflammasome, in response to MAMP (130). As a consequence of the activation of hepatic TLR and NLR, proinflammatory cytokines (IL-1β, TNFα) and chemokines, which recruit further inflammatory cells, are produced and released, thereby contributing to hepatic inflammation. Because the proinflammatory mediators are also secreted into the circulation, systemic inflammation develops, which also affects peripheral tissues.

As a consequence of elevated levels of proinflammatory cytokines arising from hepatic and systemic inflammation and of circulating MAMP, a state of hypothalamic inflammation is induced. At the molecular level, hypothalamic inflammation is induced via stimulation of the above-mentioned PRR, among which hypothalamic TLR4 is considered a major contributor (131). Stimulation of TLR4 and other PRR in the hypothalamus by LPS and cytokines results in the activation of multiple inflammatory signaling pathways, such as NF-κB, JNK/AP-1, and ER stress-induced UPR (132), thereby creating a paracrine inflammatory milieu in the hypothalamus, which modulates the activity of neuronal populations regulating appetite and energy balance (133, 134). Acute hypothalamic inflammation plays a key role in initiating the acute illness response, which represents a concerted adaptive response to infectious stimuli aiming to promote organism survival. Typical symptoms of the acute illness response, such as anorexia and cachexia, clearly indicate dysregulation of appetite and energy balance by hypothalamic inflammation.

A key mechanism underlying anorexia during acute hypothalamic inflammation is the activation of neuronal populations that produce anorexigenic neuropeptides (POMC, CART) while inhibiting hypothalamic neurons expressing orexigenic neuropeptides (AgRP, NPY), thereby decreasing appetite and food intake (133, 134). In line with this, intravenous administration of proinflammatory cytokines (IL-1β, TNFα) and LPS to livestock animals (growing pigs, broilers, lactating cows) strongly reduces feed intake and performance (gain-to-feed ratio or milk yield) (135–137). Genetically deleting any of the proteins involved in the inflammatory signaling pathways (e.g., TLR4) in the hypothalamus reduces anorexia in response to administration of LPS or cytokines (131, 138). In addition, hypothalamic inflammation—through secreting proinflammatory cytokines and through activation of the hypothalamic–pituitary axis leading to secretion of glucocorticoids such as cortisol—promotes mobilization of fuel substrates from energy stores in skeletal muscle via proteolysis and in WAT via lipolysis (139). Through this, mobilized substrates (amino acids, glycerol, fatty acids) are shifted toward tissues that are essentially required to combat infectious stimuli; e.g., amino acids in general serve as building blocks for hepatic synthesis of acute-phase proteins (140), whereas glucogenic amino acids and glycerol serve as substrates for hepatic gluconeogenesis, thereby providing immune cells with their preferential fuel substrate, glucose (53). As a result, WAT depots and skeletal muscle mass decrease, leading to typical symptoms of the acute illness response, such as cachexia and fatigue.

We and others have recently reported that the liver of livestock animals such as cows and sows develops typical signs of hepatic and systemic inflammatory conditions during early lactation as a consequence of the metabolic and physiological adaptations occurring during the transition from pregnancy to lactation (53, 54, 141–145). Because hepatic and systemic inflammation induces hypothalamic inflammation, which itself causes activation of anorexigenic hypothalamic neurons, it is not unlikely that the frequently observed reduction of food intake of livestock animals in the early lactation period is at least partially due to directly decreasing appetite in the brain.

Nevertheless, unequivocal evidence for the occurrence of hypothalamic inflammation in lactating cows and sows is lacking.

Interestingly, obesity in rodents and humans is also associated with hypothalamic inflammation (145, 146). However, obesity-associated hypothalamic inflammation is chronic and even accompanied by hypothalamic injury, as evident from gliosis (145), a nonspecific reactive change of glial cells in response to damage to the central nervous system. In this regard, several studies showed that the key site of hypothalamic inflammation and injury in high-fat diet–induced obesity is the hypothalamic ARC (145, 147), the central site for regulating appetite and satiety. Of note, in rodent models of diet-induced obesity, hypothalamic inflammation and gliosis precede the onset of body weight gain (145, 146). This indicates that hypothalamic inflammation and damage in critical regions of the hypothalamus are responsible for the altered metabolic phenotype and eating behavior of obese individuals.

Despite similar mechanisms underlying development of hypothalamic inflammation between acute illness response and diet-induced obesity, it is obvious that the feeding behavior is differentially affected by acute versus chronic hypothalamic inflammation. Burfeind et al. (139) proposed that diet-induced obesity inhibits anorexigenic neurons while activating orexigenic neurons, which is in sharp contrast to the situation in the acute illness response, in which the dominance of anorexigenic signals in the hypothalamus is responsible for induction of anorexia. In addition, several studies demonstrated that the development of hypothalamic inflammation in response to high-fat-diet feeding is accompanied by an impaired responsiveness of the hypothalamus to peripheral signals such as insulin and leptin (148, 149), both of which act as anorexigenics (150), thereby reducing food intake and body weight. Because of the obesity-induced resistance of the hypothalamus to the actions of insulin and leptin, energy homeostasis is dysregulated, and body weight gain is promoted.

CONCLUSIONS AND PERSPECTIVES

In recent years, the gut microbiota has been recognized as profoundly affecting animals' feeding behavior and energy metabolism through the ability of the gut microbiota to communicate with the animals' tissues along the gut–liver axis via different gut-derived compounds, such as SCFA, bile acids, methylamines, amino acid–derived metabolites, and MAMP. In addition, animals can shape the gut microbiota, and thereby protect the intestinal barrier—a critical component of the gut–liver axis—through secretory functions of the liver (bile acids, liver-derived IgA), as well as intestinal production of numerous antimicrobial peptides, indicating that microbiota–host communication along the gut–liver axis is bidirectional. Convincing evidence has been found that animals' food intake and energy metabolism are severely dysregulated if the intestinal barrier is impaired as a consequence of microbial dysbiosis, a condition of the gut microbiota in which microbial ecosystem balance (eubiosis) is disturbed and microbial diversity is reduced. This is explained by increased translocation of MAMP and even intact microbes into the portal and systemic circulation and subsequent induction of hepatic and hypothalamic inflammation, which causes profound derangements in the regulation of appetite and satiety in the hypothalamic ARC and in key metabolic pathways in peripheral tissues.

Because the gut microbiota composition is strongly influenced by environmental factors, such as diet, dietary interventions that promote microbial diversity and the growth of beneficial bacterial species are suitable strategies to combat microbial dysbiosis and thereby protect the intestinal barrier and prevent metabolic diseases. Suitable dietary interventions include the feeding of prebiotics (resistant starch, inulin-type fructans, cell-wall polysaccharides such as arabinoxylans, chitosan-oligosaccharides), which directly promote the growth of certain bacterial species

specialized for the degradation of selected carbohydrates but also favor microbial diversity and eubiosis through the phenomenon of cross-feeding, where typically *Bacteroidetes* species serve as primary degraders of certain polysaccharides and *Furmicutes* species further process the released products. In addition, feeding of probiotics is a promising approach to improve intestinal barrier function and metabolic health, as shown from administration of specific bacterial species such as *A. muciniphila*, which was reported to improve the gut barrier, reduce systemic inflammation, and decrease obesity in mice fed a high-fat diet (151). Furthermore, polyphenols, which include a large family of different compounds from plants, such as catechins, flavonoids, anthocyanins, and phenolic acids, are not digested in the small intestine and reach the colon, where they modulate gut microbiota composition and function by inducing antimicrobial effects and improve the intestinal barrier through microbial production of bioactive compounds.

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LITERATURE CITED

1. Brandl K, Kumar V, Eckmann L. 2017. Gut-liver axis at the frontier of host-microbial interactions. *Am. J. Physiol. Gastrointest. Liver Physiol.* 312:G413–19
2. Turner JR. 2009. Intestinal mucosal barrier function in health and disease. *Nat. Rev. Immunol.* 9:799–809
3. Abreu MT. 2010. Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function. *Nat. Rev. Immunol.* 10:131–44
4. Mantis NJ, Rol N, Corthésy B. 2011. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. *Mucosal Immunol.* 4:603–11
5. Balmer ML, Slack E, de Gottardi A, Lawson MA, Hapfelmeier S, et al. 2014. The liver may act as a firewall mediating mutualism between the host and its gut commensal microbiota. *Sci. Transl. Med.* 6:237ra66
6. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, et al. 2004. The gut microbiota as an environmental factor that regulates fat storage. *PNAS* 101:15718–23
7. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444:1027–31
8. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. 2007. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *PNAS* 104:979–84
9. Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, et al. 2005. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab.* 2:217–25
10. Mirpuri J, Raetz M, Sturge CR, Wilhelm CL, Benson A, et al. 2014. Proteobacteria-specific IgA regulates maturation of the intestinal microbiota. *Gut Microbes* 5:28–39
11. Moro-Sibilot L, Blanc P, Taillardet M, Bardel E, Couillault C, et al. 2016. Mouse and human liver contain immunoglobulin A-secreting cells originating from Peyer's patches and directed against intestinal antigens. *Gastroenterology* 151:311–23
12. Joly-Amado A, Cansell C, Denis RG, Delbes AS, Castel J, et al. 2014. The hypothalamic arcuate nucleus and the control of peripheral substrates. *Best Pract. Res. Clin. Endocrinol. Metab.* 28:725–37
13. Millington GW. 2007. The role of proopiomelanocortin (POMC) neurones in feeding behaviour. *Nutr. Metab.* 4:18
14. Cowley MA, Pronchuk N, Fan W, Dinulescu DM, Colmers WF, Cone RD. 1999. Integration of NPY, AGRP, and melanocortin signals in the hypothalamic paraventricular nucleus: evidence of a cellular basis for the adipostat. *Neuron* 24:155–63

15. Theodorakis MJ, Carlson O, Michopoulos S, Doyle ME, Juhaszova M, et al. 2006. Human duodenal enteroendocrine cells: source of both incretin peptides, GLP-1 and GIP. *Am. J. Physiol. Endocrinol. Metab.* 290:E550–59
16. Cummings DE. 2006. Ghrelin and the short- and long-term regulation of appetite and body weight. *Physiol. Behav.* 89:71–84
17. Cone RD, Cowley MA, Butler AA, Fan W, Marks DL, Low MJ. 2001. The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. *Int. J. Obes. Relat. Metab. Disord.* 25(Suppl. 5):S63–67
18. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, et al. 1995. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* 269:540–43
19. Chien EK, Hara M, Rouard M, Yano H, Phillippe M, et al. 1997. Increase in serum leptin and uterine leptin receptor messenger RNA levels during pregnancy in rats. *Biochem. Biophys. Res. Commun.* 237:476–80
20. Ehrhardt RA, Slepetis RM, Bell AW, Boisclair YR. 2001. Maternal leptin is elevated during pregnancy in sheep. *Domest. Anim. Endocrinol.* 21:85–96
21. Grattan DR, Ladyman SR, Augustine RA. 2007. Hormonal induction of leptin resistance during pregnancy. *Physiol. Behav.* 91:366–74
22. Clarke IJ, Tilbrook AJ, Turner AI, Doughton BW, Goding JW. 2001. Sex, fat and the tilt of the earth: effects of sex and season on the feeding response to centrally administered leptin in sheep. *Endocrinology* 142:2725–28
23. Miller DW, Findlay PA, Morrison MA, Raver N, Adam CL. 2002. Seasonal and dose-dependent effects of intracerebroventricular leptin on LH secretion and appetite in sheep. *J. Endocrinol.* 175:395–404
24. Klingenspor M, Niggemann H, Heldmaier G. 2000. Modulation of leptin sensitivity by short photoperiod acclimation in the Djungarian hamster, *Phodopus sungorus*. *J. Comp. Physiol. B* 170:37–43
25. Bernabucci U, Basiricò L, Lacetera N, Morera P, Ronchi B, et al. 2006. Photoperiod affects gene expression of leptin and leptin receptors in adipose tissue from lactating dairy cows. *J. Dairy Sci.* 89:4678–86
26. Cavuoto P, Wittert GA. 2009. The role of the endocannabinoid system in the regulation of energy expenditure. *Best Pract. Res. Clin. Endocrinol. Metab.* 23:79–86
27. Di Marzo V, Goparaju SK, Wang L, Liu J, Bátkai S, et al. 2001. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature* 410:822–25
28. Ravinet Trillou C, Arnone M, Delgorge C, Gonalons N, Keane P, et al. 2003. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 284:R345–53
29. Osei-Hyiaman D, DePetrillo M, Pacher P, Liu J, Radaeva S, et al. 2005. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J. Clin. Investig.* 115:1298–305
30. Matias I, Di Marzo V. 2007. Endocannabinoids and the control of energy balance. *Trends Endocrinol. Metab.* 18:27–37
31. Silvestri C, Ligresti A, Di Marzo V. 2011. Peripheral effects of the endocannabinoid system in energy homeostasis: adipose tissue, liver and skeletal muscle. *Rev. Endocr. Metab. Disord.* 12:153–62
32. Galiègue S, Mary S, Marchand J, Dussossoy D, Carrière D, et al. 1995. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Eur. J. Biochem.* 232:54–61
33. Cristino L, Palomba L, Di Marzo V. 2014. New horizons on the role of cannabinoid CB1 receptors in palatable food intake, obesity and related dysmetabolism. *Int. J. Obes. Suppl.* 4(Suppl. 1):S26–30
34. Colombo G, Agabio R, Diaz G, Lobina C, Reali R, Gessa GL. 1998. Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. *Life Sci.* 63:PL113–17
35. Cota D, Marsicano G, Tschöp M, Grübler Y, Flachskamm C, et al. 2003. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J. Clin. Investig.* 112:423–31
36. Simiand J, Keane M, Keane PE, Soubrié P. 1998. SR 141716, a CB1 cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset. *Behav. Pharmacol.* 9:179–81

37. Cluny NL, Vemuri VK, Chambers AP, Limebeer CL, Bedard H, et al. 2010. A novel peripherally restricted cannabinoid receptor antagonist, AM6545, reduces food intake and body weight, but does not cause malaise, in rodents. *Br. J. Pharmacol.* 161:629–42
38. Artegoitia VM, Foote AP, Lewis RM, King DA, Shackelford SD, et al. 2016. Endocannabinoids concentrations in plasma associated with feed efficiency and carcass composition of beef steers. *J. Anim. Sci.* 94:5177–81
39. Artegoitia VM, Foote AP, Tait RG, Kuehn LA, Lewis RM, et al. 2017. Endocannabinoid concentrations in plasma during the finishing period are associated with feed efficiency and carcass composition of beef cattle. *J. Anim. Sci.* 95:4568–74
40. Khan MJ, Graugnard DE, Loor JJ. 2012. Endocannabinoid system and proopiomelanocortin gene expression in peripartal bovine liver in response to prepartal plane of nutrition. *J. Anim. Physiol. Anim. Nutr.* 96:907–19
41. Zachut M, Kra G, Moallem U, Livshitz L, Levin Y, et al. 2018. Characterization of the endocannabinoid system in subcutaneous adipose tissue in periparturient dairy cows and its association to metabolic profiles. *PLOS ONE* 13:e0205996
42. Muccioli GG, Naslain D, Bäckhed F, Reigstad CS, Lambert DM, et al. 2010. The endocannabinoid system links gut microbiota to adipogenesis. *Mol. Syst. Biol.* 6:392
43. Karaliota S, Siafaka-Kapadai A, Gontinou C, Psarra K, Mavri-Vavayanni M. 2009. Anandamide increases the differentiation of rat adipocytes and causes PPARγ and CB1 receptor upregulation. *Obesity* 17:1830–38
44. Bouaboula M, Hilairet S, Marchand J, Fajas L, Le Fur G, Casellas P. 2005. Anandamide induced PPARγ transcriptional activation and 3T3-L1 preadipocyte differentiation. *Eur. J. Pharmacol.* 517:174–81
45. Tedesco L, Valerio A, Dossena M, Cardile A, Ragni M, et al. 2010. Cannabinoid receptor stimulation impairs mitochondrial biogenesis in mouse white adipose tissue, muscle, and liver: the role of eNOS, p38 MAPK, and AMPK pathways. *Diabetes* 59:2826–36
46. Matias I, Gonthier MP, Orlando P, Martiadis V, De Petrocellis L, et al. 2006. Regulation, function, and dysregulation of endocannabinoids in models of adipose and β-pancreatic cells and in obesity and hyperglycemia. *J. Clin. Endocrinol. Metab.* 91:3171–80
47. Tedesco L, Valerio A, Cervino C, Cardile A, Pagano C, et al. 2008. Cannabinoid type 1 receptor blockade promotes mitochondrial biogenesis through endothelial nitric oxide synthase expression in white adipocytes. *Diabetes* 57:2028–36
48. Ruiz de Azua I, Mancini G, Srivastava RK, Rey AA, Cardinal P, et al. 2017. Adipocyte cannabinoid receptor CB1 regulates energy homeostasis and alternatively activated macrophages. *J. Clin. Investig.* 127:4148–62
49. Mehrpouya-Bahrami P, Chitrala KN, Ganewatta MS, Tang C, Murphy EA, et al. 2017. Blockade of CB1 cannabinoid receptor alters gut microbiota and attenuates inflammation and diet-induced obesity. *Sci. Rep.* 7:15645
50. Maccarrone M, De Petrocellis L, Bari M, Fezza F, Salvati S, et al. 2001. Lipopolysaccharide downregulates fatty acid amide hydrolase expression and increases anandamide levels in human peripheral lymphocytes. *Arch. Biochem. Biophys.* 393:321–28
51. Liu J, Batkai S, Pacher P, Harvey-White J, Wagner JA, et al. 2003. Lipopolysaccharide induces anandamide synthesis in macrophages via CD14/MAPK/phosphoinositide 3-kinase/NF-κB independently of platelet-activating factor. *J. Biol. Chem.* 278:45034–39
52. Osei-Hyiaman D, Liu J, Zhou L, Godlewski G, Harvey-White J, et al. 2008. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. *J. Clin. Investig.* 118:3160–69
53. Bradford BJ, Yuan K, Farney JK, Mamedova LK, Carpenter AJ. 2015. Invited review: inflammation during the transition to lactation: new adventures with an old flame. *J. Dairy Sci.* 98:6631–50
54. Bionaz M, Trevisi E, Calamari L, Librandi F, Ferrari A, Bertoni G. 2007. Plasma paraoxonase, health, inflammatory conditions, and liver function in transition dairy cows. *J. Dairy Sci.* 90:1740–50
55. Zebeli Q, Metzler-Zebeli BU. 2012. Interplay between rumen digestive disorders and diet-induced inflammation in dairy cattle. *Res. Vet. Sci.* 93:1099–108

56. Ringseis R, Gessner DK, Eder K. 2015. Molecular insights into the mechanisms of liver-associated diseases in early-lactating dairy cows: hypothetical role of endoplasmic reticulum stress. *J. Anim. Physiol. Anim. Nutr.* 99:626–45
57. Zhu Y, Guan Y, Loor JJ, Sha X, Coleman DN, et al. 2019. Fatty acid-induced endoplasmic reticulum stress promoted lipid accumulation in calf hepatocytes, and endoplasmic reticulum stress existed in the liver of severe fatty liver cows. *J. Dairy Sci.* 102:7359–70
58. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. 2006. Colonic health: fermentation and short chain fatty acids. *J. Clin. Gastroenterol.* 40:235–43
59. Frankel WL, Zhang W, Singh A, Klurfeld DM, Don S, et al. 1994. Mediation of the trophic effects of short-chain fatty acids on the rat jejunum and colon. *Gastroenterology* 106:375–80
60. Bloemen JG, Venema K, van de Poll MC, Olde Damink SW, Buurman WA, Dejong CH. 2009. Short chain fatty acids exchange across the gut and liver in humans measured at surgery. *Clin. Nutr.* 28:657–61
61. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, et al. 2003. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J. Biol. Chem.* 278:11312–19
62. Thangaraju M, Cresci GA, Liu K, Ananth S, Gnanaprakasam JP, et al. 2009. GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. *Cancer Res.* 69:2826–32
63. Aguinaga Casañas MA, Schäff CT, Albrecht E, Hammon HM, Kuhla B, et al. 2017. Short communication: free fatty acid receptors FFAR1 and FFAR2 during the peripartal period in liver of dairy cows grouped by their postpartum plasma β-hydroxybutyrate concentrations. *J. Dairy Sci.* 100:3287–92
64. Friedrichs P, Saremi B, Winand S, Rehage J, Dänicke S, et al. 2014. Energy and metabolic sensing G protein-coupled receptors during lactation-induced changes in energy balance. *Domest. Anim. Endocrinol.* 48:33–41
65. Friedrichs P, Sauerwein H, Huber K, Locher LF, Rehage J, et al. 2016. Expression of metabolic sensing receptors in adipose tissues of periparturient dairy cows with differing extent of negative energy balance. *Animal* 10:623–32
66. Xiong Y, Miyamoto N, Shibata K, Valasek MA, Motoike T, et al. 2004. Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. *PNAS* 101:1045–50
67. Soliman M, Kimura K, Ahmed M, Yamaji D, Matsushita Y, et al. 2007. Inverse regulation of leptin mRNA expression by short- and long-chain fatty acids in cultured bovine adipocytes. *Domest. Anim. Endocrinol.* 33:400–9
68. Lee SH, Hossner KL. 2002. Coordinate regulation of ovine adipose tissue gene expression by propionate. *J. Anim. Sci.* 80:2840–49
69. Jiao AR, Diao H, Yu B, He J, Yu J, et al. 2018. Oral administration of short chain fatty acids could attenuate fat deposition of pigs. *PLOS ONE* 13:e0196867
70. Frost G, Sleeth ML, Sahuri-Arisoylu M, Lizarbe B, Cerdan S, et al. 2014. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nat. Commun.* 5:3611
71. Jiang L, Gulanski BI, De Feyter HM, Weinzimer SA, Pittman B, et al. 2013. Increased brain uptake and oxidation of acetate in heavy drinkers. *J. Clin. Investig.* 123:1605–14
72. Cherbut C, Ferrier L, Rozé C, Anini Y, Blottière H, et al. 1998. Short-chain fatty acids modify colonic motility through nerves and polypeptide YY release in the rat. *Am. J. Physiol.* 275:G1415–22
73. Cuche G, Cuber JC, Malbert CH. 2000. Ileal short-chain fatty acids inhibit gastric motility by a humoral pathway. *Am. J. Physiol. Gastrointest. Liver Physiol.* 279:G925–30
74. Lin HV, Frassetto A, Kowalik EJ Jr., Nawrocki AR, Lu MM, et al. 2012. Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. *PLOS ONE* 7:e35240
75. Cani PD, Dewever C, Delzenne NM. 2004. Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats. *Br. J. Nutr.* 92:521–26
76. Zhou J, Martin RJ, Tulley RT, Raggio AM, McCutcheon KL, et al. 2008. Dietary resistant starch upregulates total GLP-1 and PYY in a sustained day-long manner through fermentation in rodents. *Am. J. Physiol. Endocrinol. Metab.* 295:E1160–66

77. Gao Z, Yin J, Zhang J, Ward RE, Martin RJ, et al. 2009. Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes* 58:1509–17
78. Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, et al. 2011. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *PNAS* 108:8030–35
79. Landsberg L. 2006. Feast or famine: the sympathetic nervous system response to nutrient intake. *Cell. Mol. Neurobiol.* 26:497–508
80. Yamashita H, Maruta H, Jozuka M, Kimura R, Iwabuchi H, et al. 2009. Effects of acetate on lipid metabolism in muscles and adipose tissues of type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. *Biosci. Biotechnol. Biochem.* 73:570–76
81. Canfora EE, Jocken JW, Blaak EE. 2015. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat. Rev. Endocrinol.* 11:577–91
82. Crouse JR, Gerson CD, DeCarli LM, Lieber CS. 1968. Role of acetate in the reduction of plasma free fatty acids produced by ethanol in man. *J. Lipid Res.* 9:509–12
83. Canfora EE, van der Beek CM, Jocken JWE, Goossens GH, Holst JJ, et al. 2017. Colonic infusions of short-chain fatty acid mixtures promote energy metabolism in overweight/obese men: a randomized crossover trial. *Sci. Rep.* 7:2360
84. Jocken JWE, González Hernández MA, Hoebers NTH, van der Beek CM, Essers YPG, et al. 2018. Short-chain fatty acids differentially affect intracellular lipolysis in a human white adipocyte model. *Front. Endocrinol.* 8:372
85. Offermanns S. 2006. The nicotinic acid receptor GPR109A (HM74A or PUMA-G) as a new therapeutic target. *Trends Pharmacol. Sci.* 27:384–90
86. Plöger S, Stumpff F, Penner GB, Schulzke JD, Gäbel G, et al. 2012. Microbial butyrate and its role for barrier function in the gastrointestinal tract. *Ann. N. Y. Acad. Sci.* 1258:52–59
87. Seki E, De Minicis S, Osterreicher CH, Kluwe J, Osawa Y, et al. 2007. TLR4 enhances TGF-β signaling and hepatic fibrosis. *Nat. Med.* 13:1324–32
88. Trauner M, Boyer JL. 2003. Bile salt transporters: molecular characterization, function, and regulation. *Physiol. Rev.* 83:633–71
89. LaRusso NF, Hoffman NE, Korman MG, Hofmann AF, Cowen AE. 1978. Determinants of fasting and postprandial serum bile acid levels in healthy man. *Am. J. Dig. Dis.* 23:385–91
90. Everson GT. 1987. Steady-state kinetics of serum bile acids in healthy human subjects: single and dual isotope techniques using stable isotopes and mass spectrometry. *J. Lipid Res.* 28:238–52
91. De Boever P, Wouters R, Verschaeve L, Berckmans P, Schoeters G, Verstraete W. 2000. Protective effect of the bile salt hydrolase-active *Lactobacillus reuteri* against bile salt cytotoxicity. *Appl. Microbiol. Biotechnol.* 53:709–14
92. Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, et al. 1999. Identification of a nuclear receptor for bile acids. *Science* 284:1362–65
93. Staudinger JL, Goodwin B, Jones SA, Hawkins-Brown D, MacKenzie KI, et al. 2001. The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity. *PNAS* 98:3369–74
94. Makishima M, Lu TT, Xie W, Whitfield GK, Domoto H, et al. 2002. Vitamin D receptor as an intestinal bile acid sensor. *Science* 296:1313–16
95. Kawamata Y, Fujii R, Hosoya M, Harada M, Yoshida H, et al. 2003. A G protein-coupled receptor responsive to bile acids. *J. Biol. Chem.* 278:9435–40
96. Fujita K, Iguchi Y, Une M, Watanabe S. 2017. Ursodeoxycholic acid suppresses lipogenesis in mouse liver: possible role of the decrease in β-muricholic acid, a farnesoid X receptor antagonist. *Lipids* 52:335–44
97. Chiang JY. 2009. Bile acids: regulation of synthesis. *J. Lipid Res.* 50:1955–66
98. Kong B, Wang L, Chiang JY, Zhang Y, Klaassen CD, Guo GL. 2012. Mechanism of tissue-specific farnesoid X receptor in suppressing the expression of genes in bile-acid synthesis in mice. *Hepatology* 56:1034–43
99. Li F, Jiang C, Krausz KW, Li Y, Albert I, et al. 2013. Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity. *Nat. Commun.* 4:2384

100. Jiang C, Xie C, Li F, Zhang L, Nichols RG, et al. 2015. Intestinal farnesoid X receptor signaling promotes nonalcoholic fatty liver disease. *J. Clin. Investig.* 125:386–402
101. Sayin SI, Wahlström A, Felin J, Jäntti S, Marschall HU, et al. 2013. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metab.* 17:225–35
102. Parséus A, Sommer N, Sommer F, Caesar R, Molinaro A, et al. 2017. Microbiota-induced obesity requires farnesoid X receptor. *Gut* 66:429–37
103. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. 2008. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe* 3:213–23
104. Islam KB, Fukiya S, Hagio M, Fujii N, Ishizuka S, et al. 2011. Bile acid is a host factor that regulates the composition of the cecal microbiota in rats. *Gastroenterology* 141:1773–81
105. Inagaki T, Moschetta A, Lee YK, Peng L, Zhao G, et al. 2006. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. *PNAS* 103:3920–25
106. Kliewer SA, Mangelsdorf DJ. 2015. Bile acids as hormones: the FXR-FGF15/19 pathway. *Dig. Dis.* 33:327–31
107. Marcelin G, Jo YH, Li X, Schwartz GJ, Zhang Y, et al. 2013. Central action of FGF19 reduces hypothalamic AGRP/NPY neuron activity and improves glucose metabolism. *Mol. Metab.* 3:19–28
108. Mertens KL, Kalsbeek A, Soeters MR, Eggink HM. 2017. Bile acid signaling pathways from the enterohepatic circulation to the central nervous system. *Front. Neurosci.* 11:617
109. Higashi T, Watanabe S, Tomaru K, Yamazaki W, Yoshizawa K, et al. 2017. Unconjugated bile acids in rat brain: analytical method based on LC/ESI-MS/MS with chemical derivatization and estimation of their origin by comparison to serum levels. *Steroids* 125:107–13
110. Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, et al. 2006. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* 439:484–89
111. Broeders EP, Nascimento EB, Havekes B, Brans B, Roumans KH, et al. 2015. The bile acid chenodeoxycholic acid increases human brown adipose tissue activity. *Cell Metab.* 22:418–26
112. Katsuma S, Hirasawa A, Tsujimoto G. 2005. Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. *Biochem. Biophys. Res. Commun.* 329:386–90
113. Rath S, Heidrich B, Pieper DH, Vital M. 2017. Uncovering the trimethylamine-producing bacteria of the human gut microbiota. *Microbiome* 5:54
114. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, et al. 2013. Intestinal microbiota metabolism of *L*-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat. Med.* 19:576–85
115. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, et al. 2011. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 472:57–63
116. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, et al. 2013. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N. Engl. J. Med.* 368:1575–84
117. Gao X, Liu X, Xu J, Xue C, Xue Y, Wang Y. 2014. Dietary trimethylamine *N*-oxide exacerbates impaired glucose tolerance in mice fed a high fat diet. *J. Biosci. Bioeng.* 118:476–81
118. Chen Y-m, Liu Y, Zhou R-f, Chen X-l, Wang C, et al. 2016. Associations of gut-flora-dependent metabolite trimethylamine-N-oxide, betaine and choline with non-alcoholic fatty liver disease in adults. *Sci. Rep.* 6:19076
119. Blachier F, Mariotti F, Huneau JF, Tomé D. 2007. Effects of amino acid-derived luminal metabolites on the colonic epithelium and physiopathological consequences. *Amino Acids* 33:547–62
120. Beaumont M, Andriamihaja M, Lan A, Khodorova N, Audebert M, et al. 2016. Detrimental effects for colonocytes of an increased exposure to luminal hydrogen sulfide: the adaptive response. *Free Radic. Biol. Med.* 93:155–64
121. Bansal T, Alaniz RC, Wood TK, Jayaraman A. 2010. The bacterial signal indole increases epithelial-cell tight-junction resistance and attenuates indicators of inflammation. *PNAS* 107:228–33
122. Whitfield-Cargile CM, Cohen ND, Chapkin RS, Weeks BR, Davidson LA, et al. 2016. The microbiota-derived metabolite indole decreases mucosal inflammation and injury in a murine model of NSAID enteropathy. *Gut Microbes* 7:246–61

123. Beaumont M, Neyrinck AM, Olivares M, Rodriguez J, de Rocca Serra A, et al. 2018. The gut microbiota metabolite indole alleviates liver inflammation in mice. *FASEB J.* 33:6681–93
124. Jenne CN, Kubes P. 2013. Immune surveillance by the liver. *Nat. Immunol.* 14:996–1006
125. Gregory SH, Liu CC. 2000. $CD8^+$ T-cell-mediated response to *Listeria monocytogenes* taken up in the liver and replicating within hepatocytes. *Immunol. Rev.* 174:112–22
126. Fox ES, Thomas P, Broitman SA. 1989. Clearance of gut-derived endotoxins by the liver. Release and modification of 3H, 14C-lipopolysaccharide by isolated rat Kupffer cells. *Gastroenterology* 96:456–61
127. Atif M, Warner S, Oo YH. 2018. Linking the gut and liver: crosstalk between regulatory T cells and mucosa-associated invariant T cells. *Hepatol. Int.* 12:305–14
128. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, et al. 2007. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 56:1761–72
129. Medzhitov R. 2001. Toll-like receptors and innate immunity. *Nat. Rev. Immunol.* 1:135–45
130. Martinon F, Burns K, Tschopp J. 2002. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-β. *Mol. Cell* 10:417–26
131. von Meyenburg C, Hrupka BH, Arsenijevic D, Schwartz GJ, Landmann R, Langhans W. 2004. Role for CD14, TLR2, and TLR4 in bacterial product-induced anorexia. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 287:R298–305
132. Denis RG, Arruda AP, Romanatto T, Milanski M, Coope A, et al. 2010. TNF-α transiently induces endoplasmic reticulum stress and an incomplete unfolded protein response in the hypothalamus. *Neuroscience* 170:1035–44
133. Sergeyev V, Broberger C, Hökfelt T. 2001. Effect of LPS administration on the expression of POMC, NPY, galanin, CART and MCH mRNAs in the rat hypothalamus. *Mol. Brain Res.* 90:93–100
134. Sartin JL, Marks DL, McMahon CD, Daniel JA, Levasseur P, et al. 2008. Central role of the melanocortin-4 receptors in appetite regulation after endotoxin. *J. Anim. Sci.* 86:2557–67
135. Korver DR, Roura E, Klasing KC. 1998. Effect of dietary energy level and oil source on broiler performance and response to an inflammatory challenge. *Poult. Sci.* 77:1217–27
136. Kushibiki S, Hodate K, Shingu H, Obara Y, Touno E, et al. 2003. Metabolic and lactational responses during recombinant bovine tumor necrosis factor-α treatment in lactating cows. *J. Dairy Sci.* 86:819–27
137. Campos PHRF, Merlot E, Damon M, Noblet J, Le Floc'h N. 2014. High ambient temperature alleviates the inflammatory response and growth depression in pigs challenged with *Escherichia coli* lipopolysaccharide. *Vet. J.* 200:404–9
138. Ogimoto K, Harris MK Jr., Wisse BE. 2006. MyD88 is a key mediator of anorexia, but not weight loss, induced by lipopolysaccharide and interleukin-1β. *Endocrinology* 147:4445–53
139. Burfeind KG, Michaelis KA, Marks DL. 2016. The central role of hypothalamic inflammation in the acute illness response and cachexia. *Semin. Cell Dev. Biol.* 54:42–52
140. Andus T, Bauer J, Gerok W. 1991. Effects of cytokines on the liver. *Hepatology* 13:364–75
141. Rosenbaum S, Ringseis R, Hillen S, Becker S, Erhardt G, et al. 2012. The stress signalling pathway nuclear factor E2-related factor 2 is activated in the liver of sows during lactation. *Acta Vet. Scand.* 54:59
142. Rosenbaum S, Ringseis R, Hillen S, Becker S, Erhardt G, et al. 2012. Genome-wide transcript profiling indicates induction of energy-generating pathways and an adaptive immune response in the liver of sows during lactation. *Comp. Biochem. Physiol. D Genom. Proteom.* 7:370–81
143. Gessner DK, Gröne B, Couturier A, Rosenbaum S, Hillen S, et al. 2015. Dietary fish oil inhibits pro-inflammatory and ER stress signalling pathways in the liver of sows during lactation. *PLOS ONE* 10:e0137684
144. Gessner DK, Gröne B, Rosenbaum S, Most E, Hillen S, et al. 2015. Effect of a negative energy balance induced by feed restriction on pro-inflammatory and endoplasmic reticulum stress signaling pathways in the liver and skeletal muscle of lactating sows. *Arch. Anim. Nutr.* 69:411–23
145. Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, et al. 2012. Obesity is associated with hypothalamic injury in rodents and humans. *J. Clin. Investig.* 122:153–62
146. Guyenet SJ, Nguyen HT, Hwang BH, Schwartz MW, Baskin DG, Thaler JP. 2013. High-fat diet feeding causes rapid, non-apoptotic cleavage of caspase-3 in astrocytes. *Brain Res.* 1512:97–105

147. Valdearcos M, Robblee MM, Benjamin DI, Nomura DK, Xu AW, Koliwad SK. 2014. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. *Cell Rep*. 9:2124–38
148. De Souza CT, Araujo EP, Bordin S, Ashimine R, Zollner RL, et al. 2005. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. *Endocrinology* 146:4192–99
149. Irani BG, Dunn-Meynell AA, Levin BE. 2007. Altered hypothalamic leptin, insulin, and melanocortin binding associated with moderate-fat diet and predisposition to obesity. *Endocrinology* 148:310–16
150. Könner AC, Klöckener T, Brüning JC. 2009. Control of energy homeostasis by insulin and leptin: targeting the arcuate nucleus and beyond. *Physiol. Behav.* 97:632–38
151. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, et al. 2013. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *PNAS* 110:9066–71