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Review

Enteric Microbiota–Gut–Brain Axis from the Perspective of Nuclear Receptors

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Abstract: Nuclear receptors (NRs) play a key role in regulating virtually all body functions, thus maintaining a healthy operating body with all its complex systems. Recently, gut microbiota emerged as major factor contributing to the health of the whole organism. Enteric bacteria have multiple ways to influence their host and several of them involve communication with the brain. Mounting evidence of cooperation between gut flora and NRs is already available. However, the full potential of the microbiota interconnection with NRs remains to be uncovered. Herewith, we present the current state of knowledge on the multifaceted roles of NRs in the enteric microbiota–gut–brain axis.

Keywords: nuclear receptors; microbiota; metabolism; xenobiotics

1. Introduction

Nuclear receptors (NRs) and microbiota are two factors that together have a great impact on all body functions. With the cloning of the first NRs in the 1980s, a great era of NR research begun. The progressive discovery of the 48, 49 and 47 NRs in humans, mice and rats, respectively, and their essential role in development, metabolism, homeostasis by directing virtually each single process in these organisms, powered abundance of prospective research in this new field [1]. The prosperity of NR research partially overlapped with increasing interest in the gut microbiota and its recognized major regulatory function. An extraordinary profusion of microbiota research at the beginning of 21st century changed our perception of gut bacteria from symbiotic organisms to forming a functional "organ" modulating the host's physiological and psychological health. Within the last years, research in the field of microbiota gradually progressed from studies based on correlations between microbiota composition and diseases (e.g., autism, obesity, metabolic and autoimmune diseases) to tracking molecular pathways of interactions between specific bacterial strains, their metabolites and the host. What we have learned so far is that gut microbiota is characterized by its high variability in composition between different hosts, which is induced by multiple factors including childbirth delivery, gender, life style, diet, age, the individual's immune system, immunization, pharmacological interventions, antibiotic treatments, contacts with other carriers of bacteria, length of exposure to factors affecting bacterial composition, and geographical location [2–5]. Moreover, metabolites produced by the gut flora itself also influence microbial communities in the gut, modulating their composition, maintaining their optimal population size and protecting them from colonization by pathogens through the production of bacteriocins [6]. Recently, it has been shown that the human gut microbiota composition is influenced more by environmental factors than by the host's genome. In fact, over 20% of

inter-person microbiota variability is associated with factors related to diet, drugs and anthropometric characteristics [7]. Based on the current state of research, we can conclude that: (1) the gut microbiota is a complex and dynamic part of the body; (2) it is impossible to define a single and proper healthy gut bacteria composition that would fit all due to highly individual external and innate factors shaping distinct gut microbiota. Therefore, trying to compare and evaluate the determinants of microbiota composition is a complex task. Moreover, studies in germ-free (GF) mice have shown that the gut bacteria as an "organ" is not indispensable to live and thrive, at least in a laboratory environment. However, the regulatory function of the microbiota with specific roles in gut, brain and whole organism development and maintenance definitely represents an evolutionary benefit. During the long natural history of the symbiosis between host and microbiota, resident gut bacteria developed multiple ways of communicating with their host including with its central nervous system (CNS), which resulted in the development of a key microbiota–gut–brain axis. The aim of this article is to review existing evidence of the involvement of NRs in the interaction between host and gut microbiota, particularly in the context of the gut–brain axis.

2. Gut–Brain Axis

By now, the interaction between the gut microbiota and the brain is an evidence-based fact. Data suggest that the gut microbiota can affect physiological, behavioral and cognitive functions of the brain [8–12]. Bidirectional signaling in the enteric microbiota–gut–brain axis is regulated at neural, hormonal, and immunological levels and includes the CNS, neuroendocrine and neuroimmune systems, the enteric and autonomic (sympathetic and parasympathetic branches) nervous system, and intestinal microbiota factors. Visceral signals are transmitted directly to the CNS via afferent fibers or indirectly by the blood circulation. Response signals from the CNS are mediated via efferent fibers to the smooth muscles of the gastrointestinal (GI) tract, thereby influencing its motility and secretory functions, which modify the environment in which the bacteria reside [12–15]. Host mental state, especially under stress, has long-term effects on gut flora [16–18]. Stress increases gut permeability and modulates growth of both non-pathogenic and pathogenic bacteria via the effects of dopamine, adrenaline and noradrenaline produced by the host [19–26]. Importantly, adrenaline and noradrenaline also modulate the expression of bacterial virulence genes [26,27].

As mentioned above, gut–brain signaling works both ways; thus, signals sent by resident bacteria affect the whole body. The GI flora secrete an abundance of microbe-associated molecular patterns (MAMPs) and bioactive metabolites such as bacteriocins, secondary bile acids (BA), choline and short chain fatty acids (SCFAs). SCFAs are derived from the fermentation of polysaccharides and influence the colon epithelium locally, but also enter the blood circulation and modulate the host's incretin production and energy balance [28]. By regulating the levels of satiety and hunger hormones, including ghrelin [29,30], leptin [29,31–33], insulin [34], somatostatin [35], peptide YY (PYY) [30] and glucagon-like protein-1 (GLP-1) [36,37], bacteria affect the host's gut motility, nutrients absorption, glucose tolerance, food cravings and hunger. Stunningly, gut flora may impact the levels of hunger hormones by influencing the production of autoantibodies against peptide hormones involved in appetite control [38]. Bacterial colonization of the intestine has a major role in post-natal development and maturation of the endocrine, immune and nervous systems and affects the host's physiological and psychological health [8,39–45]. Enteric microbiota also regulates levels of sex hormones; transferring the gut microbiota of male mice to females causes an elevation in testosterone levels and induces metabolomic changes in recipient females [46]. Commensal flora itself is capable of synthesizing and releasing many neurotransmitters and neuromodulators, or inducing enteroendocrine cells to synthetize and release neuropeptides, thereby affecting the host's behavior and stress levels. Bacteria play a critical role in the production of free adrenaline in the gut lumen [47] and *Escherichia*, *Bacillus* and *Saccharomyces* spp. can generate noradrenaline [48,49]. Furthermore, the microbiota affects the hippocampus and amygdala levels of brain-derived neurotrophic factor (BDNF), a key neurotrophin involved in neuronal growth and survival [42]. *Lactobacillus* and *Bifidobacterium* species can synthetize

γ-aminobutyric acid (GABA), while *Lactobacillus rhamnosus* (*JB-1*) induces region-dependent alterations in GABA(B1b) and GABA(Aα2) receptors in various parts of the brain [45,48,49]. Importantly, vagotomized mice do not display the neurochemical and behavioral effects of *L. rhamnosus* (*JB-1*), thus implicating the vagus nerve in the direct communication between bacteria and the brain [45]. Alterations in central GABA receptor expression are implicated in the pathogenesis of anxiety and depression, which are highly comorbid with functional bowel disorders. Moreover, *Bacillus* can produce dopamine, *Lactobacillus* can generate acetylcholine, and *Candida*, *Streptococcus*, *Escherichia* and *Enterococcus* spp. synthetize serotonin (5-HT) [48,49]. 5-HT is a key regulator of GI motility and secretion but also a modulator of depression and anxiety-like behavior. Approximately 95% of 5-HT in the body is compartmentalized in the gut, predominantly in enterochromaffin cells of the mucosa and in nerve terminals of the enteric nervous system. The presence of specific strains of bacteria or the GF status in mice modulate 5-HT production by the enterochromaffin cells, which affects circulating levels of 5-HT and tryptophan, a 5-HT precursor [50–53]. Interestingly, the delivery of the probiotics *Bifidobacterium infantis* 35624, which results in an elevation in plasma tryptophan, has been suggested as a promising anti-depressive therapy [53]. Thus, the continuous dialog between the GI flora and brain—regulating parts of postnatal development, metabolism and daily body functioning—is essential for a healthy brain and gut.

3. Nuclear Receptors

NRs together form a superfamily of proteins that function as transcription factors. In principle, their activation requires the binding of ligands, which results in increased affinity towards NR-response elements in the regulatory region of target genes leading to changes in their expression activity. Multiple NRs are expressed in the GI tract, and several microbe-produced metabolites act as ligands of NRs. Thereby, the activity of NRs may be affected by nutrient- and microbiota-derived ligands. Gut bacteria secrete metabolites including indole derivatives, hormones and secondary BAs, which act as natural ligands for the host's NRs [54]. Thus, microbial metabolites influence the host by regulating gene expression that modulates biological effects. This interactive system allows a direct influence of the microbiota on the host's physiology and, therefore, it can have control over the health or disease status of the host.

3.1. PPARs

Peroxisome proliferator activated receptors (PPARs) are a sub-family of ligand-activated nuclear receptors, which consists of three isotypes; PPARα (NR1C1), PPARβ/δ (NR1C2) and PPARγ (NR1C3), each produced by a separate gene [55]. PPARs are collectively involved in the control of energy metabolism, inflammatory and immune responses. Natural ligands of PPARs include fatty acids (FA), eicosanoids and phospholipids [56,57]. Each PPAR isotype shows an individual pattern of expression in the GI tract and exerts different functions [58]. However, all three of them are known for their anti-inflammatory properties in the small intestine and colon. All PPARs mediate microbiota effects and take part in the gut–brain axis signaling; however, the way they accomplish this function is distinct (Figure 1). If their relation with the microbiota is mainly in the context of their anti-inflammatory properties, signaling to the brain is mostly related to metabolism. These two functions are highly interconnected in the GI tract as shown by our recent caloric restriction study in mice [59].

3.1.1. Peroxisome Proliferator Activated Receptor α

PPARα was initially identified as the molecular target of xenobiotics inducing peroxisome proliferation in rodents [60]. PPARα is ubiquitously expressed and is particularly abundant in organs with a high demand for catabolism of fatty acids [58]. The greatest expression of this isotype is in liver and brown adipose tissue (BAT); the stomach and duodenum also show substantial levels of PPARα. The expression of PPARα decreases along the GI tract with lowest levels in the colon [58].

PPARα coordinates several aspects of metabolism by modulating the expression of genes involved in peroxisomal and mitochondrial β-oxidation, FA transport, FA catabolism, ketogenesis and gluconeogenesis [56]. PPARα is a nutritional status sensor and allows adaptation of the rates of FA catabolism, lipogenesis and ketone body synthesis in response to nutritional status, particularly during fasting [61–63]. During the fed state, PPARα synchronizes pathways of de novo lipid synthesis to supply FAs for storage. In starvation, when the organism shifts to the mobilization of stored FAs, PPARα switches its activity to promote cellular FA uptake and β-oxidation. Moreover, PPARα stimulates the expression of rate-limiting enzymes of ketogenesis in the liver [64,65]. Importantly, the role in ketone body synthesis is dependent on the stimulation of PPARα expression in the liver by commensal gut microbiota [66]. Thus, microbiota-dependent PPARα activity modulates proper metabolic adjustment to nutrient availability. Given these facts, it is not surprising that PPARα has been identified as a major factor in the adjustment of metabolism during caloric restriction and daily rhythms (rest/activity and fasting/feeding) [59,67–70]

PPARα is a major contributor to functional circadian rhythm by directly regulating transcription of the important circadian genes *Bmal1* and *Rev-erbα* [68,71], as well as modulating PER2 activity by direct protein–protein interactions [67]. Additionally, *PPARα* itself is a target gene of BMAL1 and CLOCK [68,72]. As a result, numerous genes involved in lipid and cholesterol metabolism, as well as energy homeostasis, which are regulated by PPARα, display daily fluctuations in mouse liver [73,74]. It is noteworthy that PPARα, by mediating signals received from the microbiota via toll-like receptors (TLR), contributes to both the circadian expression of genes in the intestine and intestinal corticosterone production [75]. Thus, PPARα mediates signals from the GI flora, which impact the host's physiology.

An additional link between PPARα and microbiota has been proposed recently [76]. PPARα was identified as an important factor in the inflammatory response of the intestine to commensal microbiota. According to the model proposed, PPARα regulates the expression of interleukin 22 (IL-22) and the antimicrobial peptides Reg3β, Reg3γ, and calprotectin. In mice deficient in PPARα, commensal dysbiosis in the gut occurs and results in an increased expression of inflammatory cytokines and enhanced susceptibility to intestinal inflammation [76]. These findings comply with previous reports associating intestinal PPARα with anti-inflammatory activity in the GI tract by preventing neutrophil infiltration and protecting the intestine from colitis-induced permeability [77–80].

Even more interestingly, intestinal PPARα is involved in inducing satiety signals in the brain. Oleoylethanolamide (OEA), an endogenous ligand of PPARα, is an endocannabinoid produced by enterocytes in response to fat consumption [81]. Biosynthesis of OEA in the intestine requires sympathetic innervation [82] and is modulated by BAs [83]. Accordingly, hepatic expression of PPARα is stimulated by the farnesoid X receptor (FXR), which with the support of microbiota, controls BA metabolism (for details see the further parts of this review below) [84]. Administration of OEA has an anorectic effect by acting peripherally, prolonging eating latency or reducing meal size, depending on the nutritional state, and leads to body weight reduction [81,85–87]. This effect is mediated by PPARα activation in the proximal small intestine [81,88,89]. Surprisingly, intraperitoneal administration of OEA acutely decreases energy expenditure, as well as ambulatory and spontaneous locomotor activity [90]. It regulates lipid metabolism by activating PPARα to stimulate lipolysis, and decreases neutral lipid content in hepatocytes as well as serum cholesterol and triglyceride levels [91]. OEA in intestinal enterocytes engages afferent sensory fibers of the vagal nerve leading to increased expression of c-fos in the nucleus solitary tract (NST) and the paraventricular nucleus (PVN) of the brainstem and hypothalamus, respectively [91], which stimulates oxytocin secretion and promotes satiety [92]. Since enterocytes in the small intestine are the first cells responding to dietary fat intake by increasing OEA production, OEA was suggested to serve as a gut-derived satiety factor [81].

3.1.2. Peroxisome Proliferator Activated Receptor β/δ

PPARβ/δ is ubiquitously expressed; nevertheless, its expression in the GI tract is very high compared with other tissues. PPARβ/δ is abundant in the gut from the duodenum to the ileum,

with lesser but still detectable expression in the colon [58]. Pparβ/δ is constitutively expressed in the intestine, but inflammatory signals further stimulate its expression [93]. Intestinal PPARβ/δ induces terminal differentiation of epithelial cells in the intestine and colon and is required for the differentiation of Paneth cells [94–96]. Thus, PPARβ/δ is indirectly involved in secretion of antimicrobial peptides. PPARβ/δ protects against dextran sulphate sodium (DSS)-induced colitis [97]; however, its role in colon cancer has been controversial and conflicting results suggest that PPARβ/δ can either promote or attenuate this disease [98].

When activated, intestinal PPARβ/δ promotes fatty acid oxidation in adipose tissue and skeletal muscle, it improves dyslipidemia and stimulates overall energy expenditure thus protecting against diet-induced obesity and insulin resistance [99]. It regulates plasma HDLc levels, influences expression of genes involved in lipoprotein metabolism and stimulates postprandial GLP-1 production in enteroendocrine L-cells, resulting in preservation of pancreas β-cell morphology and function thereby increasing systemic insulin sensitivity [100]. However, the detailed mechanisms behind these beneficial properties remain to be explored further. Thus, besides enhancing the satiety signal GLP-1, no other link between intestinal PPARβ/δ and the CNS has been identified to date.

3.1.3. Peroxisome Proliferator Activated Receptor γ

PPARγ is mostly known for its insulin sensitizing properties and its role as a master regulator of adipogenesis [101]. It modulates multiple processes, including cell proliferation, differentiation, glucose and lipid metabolism, and inflammation [101–105]. PPARγ is highly expressed in adipocytes and in the gut, and at lower levels in the pancreas, liver, kidney, and immune cells. In the GI tract, it is present at a relatively high level in the proximal parts of the small intestine and gradually decreases towards its distal parts. However, it is highly expressed in the proximal colon [58,106–108]. PPARγ expression and activity are induced in the gut by multiple nutrients, most importantly by fatty acids and their metabolites but also by glutamine, curcumin, capsaicin, ginsenosides and vitamin E, all of which have been reported to exhibit anti-inflammatory properties [109]. Importantly, bacterial metabolites and bacterial by-products, such as butyrate [110,111], propionate [112] and H_2O_2 [113] also stimulate expression or activity of PPARγ. Presence of specific bacterial strains, such as *Enterococcus faecalis*, *Roseburia hominis*, *Roseburia intestinalis*, *Fusobacterium naviforme* and *Streptococcus salivarius* influence the phosphorylation of PPARγ and thereby its transcriptional activity [112,114,115]. Moreover, it has been shown that the microbiota affects liver circadian rhythm by modulating the activity of PPARγ expressed in liver [116]. Thus, there is a dynamic balance involving reciprocal interactions between PPARγ and the gut microbiota, whereby PPARγ can both be activated by bacteria and regulate the intestinal microbiota composition.

PPARγ has been identified as a promising therapeutic target in fighting colon cancer as it reduces colorectal tumor development by decreasing cell proliferation [117–119], increasing cell differentiation [117,120], inducing apoptosis [117,118,121–123], and inhibiting angiogenesis [124]. PPARγ agonists mitigate inflammatory bowel disease (IBD) symptoms, reduce inflammation, and are effective in multiple models of ulcerative colitis as well as in Crohn's disease [125–138]. PPARγ acts as anti-inflammatory mediator by regulating multiple signaling pathways, including those related to p53 [139], Bcl2 [121,123], c-Myc, [140], Cox-2 [123,141–143], Apc/B-catenin [144,145] and NF-κB [121,143]. Notably, PPARγ is responsible for the selective killing of bacteria associated with IBD and maintenance of innate antimicrobial immunity in the colon [146]. Hence, bacteria-mediated stimulation of gene activity by PPARγ appears to have a protective role in the prevention of gut inflammation and regulation of immune tolerance. Recently, we described a novel role of intestinal PPARγ in long chain FA processing in the intestinal epithelium [147]. This is an original finding given the fact that, so far, intestinal PPARγ has primarily been characterized in the context of inflammation and cancerogenesis. Importantly, using an intestinal epithelium-specific PPARγ knockout mouse model, we found a signaling mechanism between PPARγ expressed in intestinal epithelium and the brain [148]. Intestinal PPARγ in mice submitted to caloric restriction or a diet low in sucrose regulates

body adiposity by signaling via the sympathetic nerve system. Thus, activation of intestinal PPARγ by bacterial metabolites or nutrients can impact adipose tissue via the nervous system.

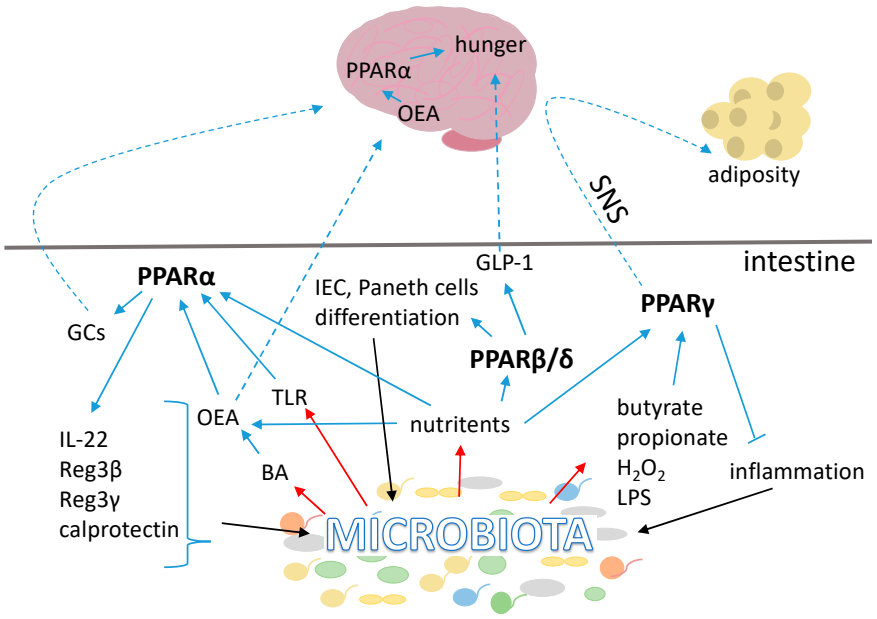

Figure 1. PPARs in gut–brain signaling. PPARs are activated by nutrient derivatives as well as bacteria-derived molecules and their signaling. PPARα serves as a receptor for oleoylethanolamide (OEA) and mediates the impact of OEA on hunger and satiety. PPARα also impacts the central nervous system (CNS) by taking part in microbiota-mediated synthesis of glucocorticoids (GCs). PPARβ/δ mediates satiety signals from gut to the CNS by stimulating the synthesis of glucagon-like protein-1 (GLP-1). Intestinal PPARγ affects adiposity via the sympathetic nervous system (SNS). Red arrows symbolize direct signals from enteric bacteria, black arrows indicate consequences of nuclear receptor (NR) signaling on the bacteria and blue arrows illustrate interactions between the pictured factors. Blue solid lines correspond to interactions within intestine or the brain while blue dotted lines mark signaling between the organs.

3.2. Farnesoid X Receptor (FXR)

BAs produced by the liver are stored in the gall bladder and secreted into the small intestine where they contribute to the emulsification and solubilization of fats. Thus, they aid in the digestion and absorption of lipids. The expression profile of genes involved in BA synthesis, conjugation, and reabsorption is altered by the resident gut microbiota [149]. Certain secreted BAs undergo biotransformation by the gut microbiota from primary to secondary BAs [150], and this process is accompanied by a feedback mechanism of BAs on the microbiota composition [151,152]. Moreover, secondary BAs, but also some of the primary BAs, can act as ligands for the nuclear receptor FXR (NR1H4), which is expressed in enterocytes throughout the small intestine and colon [153]. BA activation of FXR leads to subsequent alteration of the BA pool size via two FXR-dependent feedback mechanisms of hepatic BA synthesis [154]. FXR regulates the transcription levels of critical genes in BA synthesis, homeostasis, transport and metabolism [155] but also affects general lipid and glucose metabolism [156], as well as hepatic autophagy [157,158]. Mice lacking FXR expression in the intestine withstand diet-induced obesity (DIO), insulin resistance and non-alcoholic fatty liver disease, and several studies associated FXR with sensitivity to metabolic diseases [149,159–162]. FXR knockout may be mimicked by a treatment with tempol (4-hydroxy-2,2,6,6-tetramethyl-piperidine-*N*-oxyl) a stable nitroxide which is a membrane-permeable, and metal-independent superoxide dismutase (SOD) mimetic. Tempol decreased the *Lactobacillus* population in gut, accompanied by reduced activity of bile salt hydrolase (BSH) normally exhibited by the bacteria. As a result, a potent antagonist of FXR,

tauro-β-muricholic acid (T-β-MCA) accumulated in the intestine, demonstrating that the enteric flora can modulate the activity of FXR [159]. Moreover, the gut microbiota has been shown to promote DIO and stimulate adiposity via activation of the intestinal BA/FXR axis, which contributes to alteration of the ceramide/SREBP1C/CIDEA pathway in the liver and disrupts lipid homeostasis [149,160]. Conversely, FXR may contribute to increased adiposity by modulating the composition of the gut microbiota [149]. Thus, the tie between FXR and microbiota is tight and complex and, therefore, difficult to dissect. However, it is sufficiently documented that targeting bacteria or BA composition can result in changes of FXR activity and body weight.

A link was identified between the BAs in the gut and cystic breast tissue in humans [163,164]. The bile salt lithocholate originating from the intestine was found in aspirates of cyst fluid from the breasts of women with fibrocystic disease at much higher concentrations than in the serum [163]. Additionally, BAs such as deoxycholic acid (DCA) have been shown to stimulate both the growth and metastasis of breast cancer cells through FXR expressed in the breast cancer tissue [165], suggesting that BAs may play a role in breast tumor carcinogenesis.

Among other genes, FXR binds a response element in the regulatory region of *Fgf15* (a rodent ortholog to human *Fgf19*) and directly regulates its transcription. FGF15 is produced in the distal small intestine, and is secreted into the portal circulation to function as a postprandial hormone [166,167]. Its levels rise following a meal with a lag comparable to that of insulin. In contrast to other enterokines (e.g., GLP-1, GIP), FGF15 does not affect insulin secretion but rather mimics insulin impact [167,168]. The peak of FGF15 occurs 90–120 min after the postprandial release of BAs, precedes the repression of BA synthesis [167], and causes the gallbladder to refill with bile [169]. Secreted FGF15 circulates to the liver, where it acts on two receptors: FGF-receptor 4 (FGFR4) and β-Klotho (KLB). This results in the activation of the Ras–ERK–p90RSK pathway, which affects the expression of genes, such as *c-Fos*, *JunB*, and *c-Jun* [168,170]. FGF15 inhibits BA synthesis in the liver by repressing the transcription of the cholesterol 7α-hydroxylase gene (*Cyp7a1*), which encodes the first and rate-limiting enzyme in the classic BA synthesis pathway [171]. FGF15 also stimulates hepatic protein and glycogen synthesis [172], contributes to the regulation of systemic lipid and glucose metabolism [173] and represses gluconeogenesis through a mechanism involving the dephosphorylation and inactivation of the transcription factor CREB [174]. Importantly, according to the current state of knowledge FGF15 represents a key factor in the FXR–gut–brain axis connection. FGF15 secreted from the intestine leads to activation of its receptors in hypothalamic AGRP/NPY neurons leading to reduction of signaling by these neurons. This regulation promotes glucose tolerance presumably mediated by the autonomic nervous system [175]. Thus, FGF15 can modulate metabolism by acting directly on the brain, which is supported by the observation according to which intra-cerebro-ventricular injection of FGF15 reduces 24 h food intake and body weight, and acutely improves glucose tolerance [176]. In *ob/ob* mice, FGF15 administered centrally increases glucose disposal via an insulin-independent mechanism [177]. Remarkably, FGF15-triggered nerve signaling is required for longer-term weight loss and glycemic effects while its activity in the liver and adipose tissue is not [178]. Notably, expression of human FGF19-receptors 1 and 4 in the hypothalamus of obese rats is reduced by 60% relative to lean animals [176]. It has been shown that intestinal PPARα affects FXR-FGF15 activity and BA synthesis [179] and BA feedback inhibits PPARα activity [180]. Thus, we can speculate that gut–brain communication involves the microbiota and at least two NR networks, in other words a microbiota–PPARα–FXR–FGF15–gut–brain axis.

3.3. Vitamin D Receptor

Synthesis of vitamin D is initialized when UVB light triggers photochemical, non-enzymatic conversion of 7-dehydrocholesterol to previtamin D_3 in keratinocytes of the skin. Consecutively previtamin D_3 undergoes thermal isomerization to vitamin D_3 (cholecalciferol). Following circulation in the bloodstream, vitamin D_3 is taken up by liver and modified to the prohormone calcifediol (25-hydroxyvitamin D_3, 25(OH)D_3). Additionally, vitamin D_2 or ergocalciferol, which can be provided

by nutrition, including sources like fish, egg and mushrooms, serves as another precursor that may be modified to calcifediol. Further conversion of calcifediol into calcitriol (1,25-dihydroxyvitamin D, $1,25(OH)_2D$) is executed by 1α-hydroxylase (CYP27B1) and takes place mostly in the kidneys. Nonetheless, 1α-hydroxylase is also expressed in other tissues including colon, breast tissue and immune cells [181–185]. Levels of vitamin D in the blood show a strong relationship with infection rates, bone health, cancer prophylaxis and mortality [186–190]. Calcifediol and calcitriol serve as ligands for the vitamin D receptor (VDR, NR1I1), the second being a more potent activator [191]. Additionally, the secondary bile acid lithocholic acid, curcumin, γ-tocotrienol, and derivatives of essential fatty acids also act as ligands of VDR [192,193]. Upon activation by ligands, VDR activates or represses expression of its target genes. VDR is particularly important for the homeostasis of minerals by regulating the intestinal uptake of calcium, iron, magnesium, zinc, copper and selenium. VDR also regulates calcium reabsorption in kidneys and promotes bone calcification. Notably, VDR also facilitates intestinal absorption of toxic elements like lead, aluminum, cadmium, cobalt and strontium [194]. VDR is expressed throughout the body with high levels in the intestine, colon, thyroid gland and kidney. Its expression in the brain remains to be clarified as there are contradictory reports on this subject [195–197]. Importantly, vitamin D can barely diffuse through the blood brain barrier (BBB) [198] however, 1α-hydroxylase is expressed in the CNS [199,200] suggesting a role in the brain.

VDR plays an important role in the immune response, mediates signals from the microbiota and translating them into appropriate inflammatory responses [201–203]. VDR influences the expression of defensins, the antimicrobial function of Paneth cells and colonization of the GI tract by bacteria [204–206]. Consequently, the microbiota of VDR knockout mice differs when compared to wild type mice [207]. Intestine epithelium-specific VDR knockout mice are also more susceptible to DSS-induced colitis [206]. The TLR pathway when activated by pathogen-associated membrane patterns (PAMPs) of *Mycobacterium tuberculosis* stimulates VDR expression. In turn, VDR is necessary for the generation of the antimicrobial peptides cathelicidins by monocytes-macrophages and the killing of intracellular *Mycobacterium tuberculosis* [208,209]. Moreover, the probiotic *Lactobacillus rhamnosus* strain GG and *Lactobacillus plantarum* trigger the expression and transcriptional activity of VDR and thereby protect from *Salmonella*-induced colitis in a VDR-dependent way [210]. Reciprocally, microbiota regulates local production of vitamin D_3 in the colon by signaling through the TLR pathway [211].

VDR is a vital factor in brain development [212], neurotransmission [213], neuroprotection [214,215] and immunomodulation [216,217]. Vitamin D deficiency has been linked with occurrence of autism [218,219], schizophrenia [220–222], multiple sclerosis [223,224], Alzheimer's and Parkinson's disease [225]. However, the putative mechanisms linking VDR to neurological diseases remain to be unveiled. Moreover, a direct role of VDR in the gut–brain axis has not been established so far.

3.4. Xenobiotic Receptors

3.4.1. Aryl Hydrocarbon Receptor

Aryl hydrocarbon receptor (AHR) is not per se a member of the NR superfamily, although it shares many characteristics with family members. AHR is a ligand-activated receptor expressed in many cell types, including intestinal epithelial cells (IEC). AHR is mostly recognized as a molecule activated by the xenobiotic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, also known as dioxin) [226,227]. However, the list of its agonists is much longer and contains various groups of molecules including diet-derived compounds (e.g., flavonoids, carotenoids, stilbenes) [228–230], metabolites of tryptophan produced by the host, such as kynurenine (KYN) [231] or kynurenic acid (KYNA) [232], and by the microbiota (indoles) [233,234]. Also, phenazine produced by *Pseudomonas aeruginosa*, and naphthoquinone phthiocol from *Mycobacterium tuberculosis* bind to AHR, which triggers cytokine and chemokine production [235]. Moreover, the bacterial metabolites SCFAs modulate AHR activity, however not directly as ligands, but they stabilize and facilitate AHR actions [236]. Intestinal AHR affects the differentiation and function of T cells, macrophages, and dendritic cells [237–244]. AHR expressed

in CD11c$^+$ cells modulates the development of intestinal epithelium and intestinal immunity [245] thus, in turn it may modulate gut microbiota composition. Expression of AHR is attenuated in GF mice and AHR seems to mediate the impact of microbiota on the host's metabolic parameters. Hence, AHR has been suggested to act as a mediator in the communication between the host and its gut microbiota [246]. The most evident interaction between microbiota and AHR comes from a study on the caspase recruitment domain family member 9 (CARD9). CARD9 promotes recovery from colitis by stimulating interleukin (IL)-22 production. Hence, *Card9*$^{-/-}$ mice are more susceptible to colitis. Interestingly, the *Card9*$^{-/-}$ mice-specific microbiota fails to metabolize tryptophan into compounds acting as AHR ligands. Transfer of these bacteria to wild-type GF recipients increases their susceptibility to colitis. Intestinal inflammation in these transfer recipients is attenuated after inoculation of the mice with three *Lactobacillus* strains capable of metabolizing tryptophan or by treatment with an AHR agonist [247]. Thereby, host expression of genes like *Card9* affects the microbiota pool and this regulation feeds back on the host's health-status.

In the liver, PPARα and AHR affect the expression of a similar set of genes including *Cd36*, *Hmgcs2* [246,248], *Cyp2B*, *Cyp3A*, *Cyp2C11* [249] and *Fgf21* [65,250,251], indicating that there is an interplay between these two factors, which has been investigated [249,252–254]. FGF21 has been identified as the mediator of the metabolic benefit of AHR [251]. In turn, the impact of FGF21 on metabolism is partly mediated by PPARγ [255] creating a feed-forward loop as PPARγ also induces FGF21 expression [256]. FGF21 stimulates the expression of genes involved in lipid oxidation, ketogenesis and gluconeogenesis [65,257,258]. FGF21 improves insulin and leptin sensitivity and lowers blood glucose levels by activating glucose uptake in adipocytes. Its administration results in reduced body weight due to enhanced energy expenditure, fat oxidation and lipid excretion, while reducing hepatic *de novo* lipogenesis and hepatosteatosis [251,259,260]. Similarly to FGF15, the role of FGF21 in metabolism and body weight regulation seems to require mostly its central, rather than peripheral signaling [178,261,262]. Along these lines, microbiota-stimulated AHR may regulate metabolism via FGF21-mediated signaling to the CNS. Interestingly, in response to sugar consumption, hepatic FGF21 is released and attenuates sugar-seeking behavior by targeting the hypothalamic PVN [263,264]. Activation of FGF21 upon sugar uptake is mediated by hepatic PPARα and carbohydrate-responsive element-binding protein (ChREBP) [263]. Beside affecting metabolism, FGF21 regulates hydration by suppressing alcohol intake in favor of water consumption and this activity is mediated in part by SIM1-positive neurons in the hypothalamus [265].

AHR is widely expressed in the CNS [266,267] and plays there a multitude of roles in cell differentiation and maintenance. AHR-1, a *Caenorhabditis elegans* orthologue of AHR, is responsible for the development, orientation, and axonal migration of AHR-1-expressing neurons [268]. AHR-1 impacts neural cell fate determination in *C. elegans*, particularly GABAergic neurons [269]. Dioxin-activated AHR plays a role in CNS development in zebrafish [270] and mice [271,272]. However, expression of a constitutively active AHR in mice retards the development of interneurons in the olfactory bulb [273]. Furthermore, both deletion or activation of AHR alters adult hippocampal neurogenesis and impairs hippocampal-dependent contextual memory [274], suggesting a need for a balanced AHR activity. AHR has been shown to affect several aspects of behavior and neurodevelopmental illness in different study models [275,276]. AHR has been shown to decrease blood brain barrier (BBB) permeability [277,278], while BBB permeability is increased in GF mice [279]. However, the mechanism behind is not clear as AHR is capable of activating occludin and claudin 1 and 4 [280], but on the other hand it inhibits connexin 43 [281], which is essential for BBB integrity [282]. This is probably another example of the dual role of AHR, which again underlines the importance of a balanced activation of AHR. Moreover, AHR mediates anti-inflammatory effects on dendritic cells [283]. Ligand-activated microglial AHR exerts bi-directional effects on the regulation of LPS-induced neuroinflammation as it can promote or inhibit inflammation [284,285]. Notably, in patients with multiple sclerosis circulating levels of AHR agonists are decreased [286].

The effects of AHR expressed in CNS can be modulated by the microbiota [286]. Astrocytes are the most abundant glial cell population in the CNS, participating in diverse functions including control of the BBB, regulation of metabolism, neuronal transmission, CNS development and inflammation [287]. In experimental autoimmune encephalomyelitis (EAE), type 1 interferon (IFN-I) signaling in astrocytes reduces disease scores and inflammation via AHR and the suppressor of cytokine signaling 2 (SOCS2). EAE scores in mice increase following ampicillin treatment, whereas dietary supplementation with the microbial metabolites of tryptophan (indoxyl-3-sulfate, indole-3-propionic acid and indole-3-aldehyde)—which as mentioned above are AHR ligands—or delivery of the bacterial enzyme tryptophanase reduces CNS inflammation in the antibiotic treated mice. Thus, IFN-Is produced in the CNS functions in combination with bacterial metabolites of dietary tryptophan to activate AHR signaling in astrocytes and suppress CNS inflammation [286].

3.4.2. Pregnane X Receptor

Pregnane X receptor (PXR, NR1I2) also known as the steroid and xenobiotic sensing nuclear receptor (*SXR*) is a nuclear transcription factor often referred as the master regulator of xenobiotic defense. PXR is involved in energy [288,289] as well as xenobiotic metabolism and it affects expression of phase I and phase II enzymes as well as phase III transporters [290]. PXR is expressed in barrier and excretory tissues, including intestine, liver, kidney and several regions of the brain [290–292] and it is synthetized as various splice variants in different organs [292–294]. In the liver, the function of PXR overlaps with that of FXR by regulating expression of a similar set of CYP proteins involved in both detoxification and BA metabolism. Additionally, other PXR target genes that are involved in xenobiotic metabolism also participate in BA metabolism [295]. In primary human hepatocytes, among other factors PXR regulates AHR and its target genes *Cyp1A1* and *Cyp1A2* [296]. Similarly to AHR, PXR is activated by microbial-specific metabolites of dietary tryptophan, and the indole derivative, indole 3-propionate (IPA) [297], which is produced by *Clostridium sporogenes* [52]. The ligand binding pocket of PXR has a relatively large volume capable of accommodating a variety of compounds. Moreover, PXR has the capability to expand its binding pocket to allow for larger compounds thus, various ligands are capable of its activation [298].

Secondary BAs, lithocholic acid (LCA) and its 3-keto metabolite (3-keto LCA), formed in the intestine by bacteria are ligands of mouse and human PXR [295,299]. LCA is a particularly toxic BA that causes cholestasis, a disease characterized by the impairment of bile flow and the accumulation of BA and biliary toxins in the liver and serum [300]. Moreover, pregnenolone 16α-carbonitrile (PCN), a ligand of PXR, blocks the hepatotoxicity and mortality caused by LCA exposure in rats [299,301]. Therefore, PXR, among other ligands, serves as a receptor of BA and upon activation coordinates the xenobiotic response in the detoxification of BAs.

Single nucleotide polymorphisms in *Pxr* are associated with increased susceptibility for developing IBD, Crohn's disease and ulcerative colitis [302]. While PXR-deficient mice exhibit "leaky" intestine symptoms [297], ligand-activated PXR prevents leaky gut and maintains the intestinal epithelial barrier by stimulating the synthesis of junctional proteins, antagonizing TNF-α and TLR4, inhibiting the cytokine-induced myosin light chain kinase (MLCK), and activating the c-Jun N-terminal kinase$\frac{1}{2}$ (JNK1/2) [291,297,303,304]. Rifaximin, an antimicrobial agent used in the treatment of IBD, mediates its effects by increasing the expression of PXR. It has been shown to abrogate the DNA binding of NF-κB caused by LPS, to reduce mRNA levels of IL-8, RANTES, MIP-3α and TNFα [305]. Chrysin, a naturally occurring flavonoid with anti-inflammation activity, prevents DSS-induced colitis, an effect largely mediated by PXR [306]. Furthermore, the above mentioned PXR agonist, PCN, attenuates the intestinal barrier dysfunction observed after DSS administration in mice [304].

Absence of PXR is associated with anxiety-like behavior and recognition memory impairment in adult mice [307]. PXR knockout (KO) mice show decreased expression of tight junction protein ZO1 in the cortex and cortical microvessels [307]. In another study, activation of hPXR in mice in vivo tightened the BBB, reducing the delivery and central effect of administrated drugs. This effect is

mediated by PXR-stimulated upregulation of P-glycoprotein, an ATP-driven drug export pump at the BBB [308]. P-glycoprotein is the most prominent drug efflux transporter at the BBB and plays an essential role in barrier function. Hence, most likely, similarly to AHR, microbiota derived-ligands regulate PXR activity in CNS, thus affecting the BBB.

3.4.3. Constitutive Androstane Nuclear Receptor (CAR)

CAR (NR1I3) or constitutive androstane nuclear receptor, alike AHR and PXR, serves as a xenosenor. CAR expression level is affected by various factors. It is induced on the level of expression or activity by glucocorticoids (GC) [309], AHR [310], peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) [311] and repressed by factors like epidermal growth factor (EGF) [312], TLR-2 signaling [313] and IL-1β [314]. Beside xenobiotics, CAR can be regulated by many endobiotics, including many steroids (androstanes, estrogens, and progestins) [315,316]. Importantly, expression of CAR in the intestine and in the liver depends on the presence of the microbiota [313,317]. CAR was originally characterized as a transcriptional regulator whose activation is stimulated by phenobarbital (PB) to stimulate the expression of *CYP2B* genes [318,319]. By now, the list of both the activators and target genes of CAR has significantly expanded and shows a high overlap with the corresponding list for PXR. These two NRs are often described together as both are expressed in organs like the small intestine, colon and liver. They both react to chemical stresses and are crucial to initial ligand recognition followed by subsequent jump-starting of xenobiotic metabolism. They work together to ensure homeostasis of cholesterol, BAs, sterols, lipids, heme and other endogenous hydrophobic molecules. Furthermore, the different splice variants of CAR, similarly to those of PXR, result in a number of deleterious or altered effects on gene transactivation, coregulator recruitment, as well as ligand binding [296,320–323]. Although CAR is less promiscuous than PXR, the smaller pocket size of CAR creates a more stable ligand-bound complex than the one of PXR, resulting in better packing of the AF-2 helix in the active conformation [324]. However, CAR is unique, relative to other NRs, in its ability to maintain a constitutive activity in the absence of a bound ligand. This ability is also referred to as an indirect activation, the exact mechanism of which remains to be elucidated [325,326]. In its inactive form, CAR, just like PXR, is bound to heat shock protein 90 (Hsp90) in the cytoplasm [327]. Upon activation and heterodimerization with the retinoid X receptor (RXR) it stimulates target gene expression in the cell nucleus [328]. A notable feature recently highlighted for CAR is that upon ligand binding it can also undergo translocation to cell membrane, which could imply additional non-genomic actions [329].

Notably, because CAR and PXR can be activated by the same ligands, upregulation of overlapping sets of genes allows for coordinated clearance and detoxification of harmful compounds [296,330]. Importantly, some drugs inhibiting CAR are agonists of PXR, thus allowing detoxification to take place even in the absence of one of the sensors. Together, the two NRs regulate expression of phase I enzymes of xenobiotics metabolism including CYP3As [331,332], CYP2Bs [319,332–334], and CYP2Cs [332,335,336]. They are capable of regulating approximately 90% of all phase II metabolic enzymes as both are involved in the transcriptional control of UDP-glycosyltransferases (UGTs), sulfotransferases (SULTs), glutathione-*S*-transferases (GSTs), acetyltransferases [324,337] as well as the drug transporters OATP1 and MDR1 involved in phase III detoxification [332].

CAR has also been linked to energy metabolism as its activation results in inhibition of lipogenesis, FA synthesis, and gluconeogenesis, as well as the increase of energy expenditure in BAT [338]. Long-term CAR activation improves glucose homeostasis and insulin sensitivity [339]. These effects are achieved by suppressing the expression of phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6Pase) [339,340], and sterol regulatory element-binding protein 1c (SREBP1c) [341]. A very similar phenotype has been associated with PXR activation [288,289,342]. Moreover, fasting and caloric restriction induce CAR expression, which in turn coordinates an adaptive response by slowing down energy expenditure. Consequently, CAR KO animals are

unable to accomplish the metabolic adjustment and lose more weight during caloric restriction interventions [343].

In the intestine, *CAR* gene expression is reduced in intestinal mucosal biopsies obtained from patients suffering from Crohn's disease or ulcerative colitis with active mild or moderate inflammation, as well as in tissues isolated from colitic mice. Selective activation of CAR enhances wound healing in IEC monolayers in culture, an effect driven by enhanced cell migration. Finally, inhibition of CAR delays mucosal healing after the induction of experimental colitis, while its pharmacological activation accelerates recovery [344]. Thus, by affecting colonic health, CAR alters the natural milieu of the microbiota.

Notably, as shown by using null mice, CAR affects structural factors in the brain and the behavior of mice. These CAR-null animals show impairment in recognition memory and increased anxiety-like behavior, which is accompanied by neuronal and structural defects in the hippocampus and cortical area. Moreover, expression of the tight junction protein ZO-1 is reduced in cortical and hippocampal microvessels of the animals. Accordingly, peripheral injection of the neurotoxin kainic acid provokes a rapid onset of convulsions in CAR-null mice as compared to WT mice, indicating increased vascular permeability and susceptibility of these mice to neurotoxins [345].

In conclusion, gut flora modulates CAR activity, and CAR feeds back by reducing and promoting gut inflammation and healing, respectively. There is no evidence of direct gut–brain communication involving CAR. However, the CAR–microbiota interaction in gut, CAR's role in the brain, and the importance of other xenobiotic receptors in gut–brain signaling provide a basis to speculate on a potential CAR-mediated signaling between the GI tract and CNS.

It seems that all of the xenobiotic receptors–AHR, PXR and CAR—interact with microbiota, and are required for the proper functioning of the brain (Figure 2) [346,347]. Importantly, these NRs are interconnected and show high level of coordination, and thus future research may show that they embody an essential pathway in gut–brain communication.

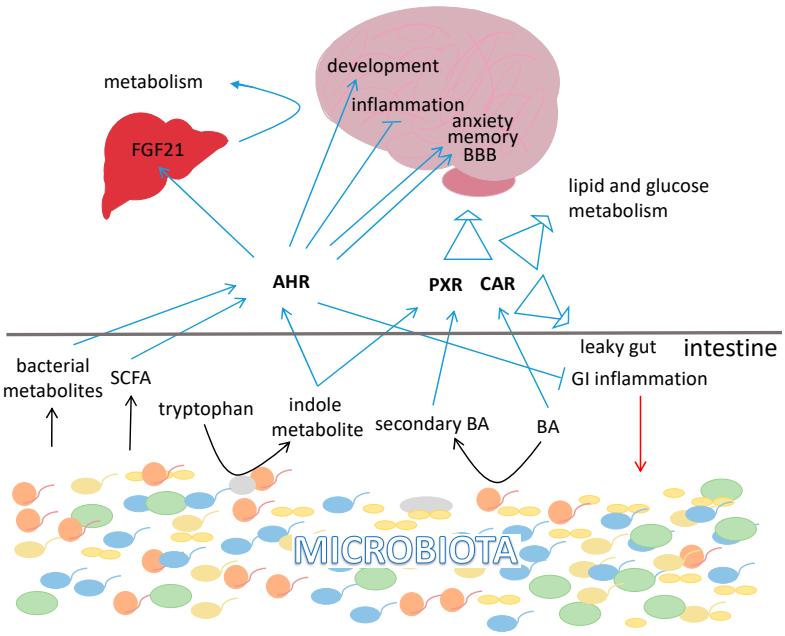

Figure 2. Xenobiotic receptors in the gut-brain axis. Bacterial metabolites, mainly indole and bile acids (BA) serve as ligands for xenobiotic receptors. These NRs play multifold roles in the brain by affecting the CNS development, permeability of the blood-brain barrier (BBB), memory and anxiety. Broad blue arrows illustrate the action of both PXR (pregnane X receptor) and CAR (constitutive androstane nuclear receptor), narrow blue arrows the actions of single factors, black arrows indicate bacteria-derived signals and the red arrow the impact of GI inflammation on the microbiota.

3.5. Steroid Receptors

3.5.1. Glucocorticoid Receptor

The main steroids of the adrenal cortex are mineralocorticoids (MCs), glucocorticoids (GCs in humans mainly cortisol and in rodents mainly corticosterone) and the adrenal androgens. GCs are synthesized and released as a result of stress, but also in a daily oscillating manner [348]. The circadian release of GC can be maintained regardless of sleep pattern, light stimulation and rhythm of caloric intake [349,350]. Coordinated release of GCs, mineralocorticoids and catecholamines by the adrenal glands in response to stress is governed by the hypothalamic–pituitary–adrenal (HPA) axis, also referred to as the "stress axis". Signals such as daylight promote the release of corticotrophin-releasing hormone (CRH) from the hypothalamus. CRH then stimulates the production of the adrenocorticotropic hormone (ACTH) in the pituitary, which in turn, initiates release of GC from the adrenal cortex to blood. As GC levels rise, a negative feedback loop is engaged that reduces both CRH and ACTH expression and secretion. This feedback mechanism regulates the magnitude and duration of GC release [351].

Although endogenous GCs are predominantly produced by the adrenal glands, there is evidence for extraadrenal GCs synthesis in the skin [352], thymus [353,354], vascular wall [355], lungs [356], brain [357] as well as IEC [358]. More specifically, liver receptor homologue-1 (LRH-1) in the cells of the crypt region of the intestinal epithelial layer promotes the expression of steroidogenic enzymes and the synthesis of corticosterone [358]. Additionally, immune stress and T cell activation are also stimulators of intestinal expression of the steroidogenic enzymes required for GC synthesis [359]. Importantly, the microbiota contributes to the production of corticosterone in the intestine [75] and influences the intracellular activity of GCs [360].

GCs are essential primary stress response hormones necessary for regulating numerous physiological processes in order to maintain homeostasis, and they reduce inflammation. Overall, their major effect on glucose homeostasis is to secure plasma glucose levels for brain during stress [361]. However, GCs also mediate multiple other physiological processes, including metabolic homeostasis, skeletal growth, cardiovascular function, reproduction, and cognition [362–364]. Synthetic derivatives of these hormones serve in the clinics as a standard treatment for inflammatory diseases, autoimmune disorders and hematologic cancers. Depending on the concentration of GCs, different receptor responses are triggered. Basal plasma levels of GCs are mediated via the mineralocorticoid receptors (MRs, NR3C2) (see below), while elevated, stress or circadian rhythm-triggered GCs activate the glucocorticoid receptors (GRs, NR3C1) [365,366]. The GR is expressed in almost every cell in the body and in multiple brain regions including the cerebral cortex, olfactory cortex, hippocampal formation, amygdala, septal region, dorsal thalamus, hypothalamus, trapezoid body, cerebellar cortex, locus coeruleus and dorsal raphe nucleus [367,368]. GR is encoded in a single gene, however, there are multiple GR protein isoforms. Alternative splicing of the 3′-end of the GR pre-mRNA produces GRα, GRβ and GRγ [369–371]. Moreover, alternative translation initiation from the single GRα mRNA transcript produces an additional eight diverse GRα proteins [372]. This substantial group of functionally distinct receptor subtypes undergoes various posttranslational modifications that further diversifies their signaling properties [373–375]. In the cytoplasm, GC-activated GR is released from a multiprotein complex composed of HSPs and immunophilins of the FK506 family [376,377] then translocates to the cell nucleus and modulates gene transcription via the following three mechanisms: GC receptor response element (GRE)-mediated direct transactivation; inverted repeat GREs (IR nGREs)-mediated direct transrepression; and tethered indirect transrepression [378–384]. The capacity of the GR to function as a transcriptional activator or repressor is determined by several polymorphisms in the GR gene [385]. GR can also modulate mRNA splicing [386] and mRNA stability [387] as well as microRNA expression and processing [388]. MR and GR can create homodimers or heterodimers acquiring new transcriptional properties [389,390]. Moreover, GR exhibits nongenomic signaling by direct protein–protein interactions that result in rapid cellular responses occurring within a few

seconds to minutes, which involve the signaling cascade of various kinases and do not require changes in gene expression [380,391–393]. The various GR forms and their signaling modes generate pleiotropic effects in distinct tissues [394,395].

GCs and circadian rhythm factors are reciprocally regulated. The central circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus entrained by light received by the retina orchestrates diurnal rhythmic oscillation of circulating GCs by influencing the activity of the HPA axis [396,397]. Additionally, the circadian rhythm core transcription factor heterodimer Clock-Bmal1 acetylates GR in peripheral tissues and represses its transcriptional activity in a circadian pattern that is opposite to the GR activation pattern by the HPA axis [398]. In return, the HPA axis, through the GR, drives circadian and ultradian bursts of transcriptional activity of the circadian rhythm regulators (Per 1, DBP) and adjusts the rhythmicity of the peripheral clocks in response to stressors [396,399]. Thus, the circadian rhythm of the peripheral clocks may become phase-shifted by GCs. Disruption of GR expression periodicity is associated with disease states characterized by GC resistance or sensitivity [400]. Moreover, cortisol-driven circadian and ultradian patterns of transcriptional activity of the *Clock* and *Per* genes is disrupted in major depressive disorders, bipolar disorder, and stress-related GI and immune disorders [401]. Furthermore, intestinal processes including nutrient absorption, cell proliferation, intestinal motility, metabolic activities as well as intestinal GC production are rhythmically regulated in a circadian manner [75,402]. Clock genes are expressed along the GI tract, their mRNA levels increase from the duodenum onwards and show highest levels in the colon. Similar to other organs, the clock genes in the jejunum and colon show a circadian rhythm of expression [403–405]. Moreover, the intestinal microbiota exhibits endogenous circadian rhythmicity that is partly synchronized with the host's dietary rhythm [406–408]. Remarkably, gut microbiota-derived MAMPs, acting via TLR, regulate circadian clock genes and PPARα and thereby modulate the production of intestinal corticosterone [75]. Moreover, microbial cycles disturbed by a high-fat diet results in disruption of the central and liver clocks [407].

GR regulates multiple systems including the nervous, cardiovascular, musculoskeletal, immune, respiratory, reproductive, adipose and hepatic systems. It adjusts blood glucose levels by stimulating hepatic gluconeogenesis via direct induction of the *PEPCK* gene [409]. It suppresses bone formation by a number of mechanisms, including reduction of osteoblast differentiation [410], induction of osteoblast apoptosis [411], and stimulation of bone resorbing osteoclasts [412]. In adipocytes, it increases adipogenesis, alters adipokine production, reduces glucose metabolism and lipogenesis under basal or fasted conditions, while it stimulates lipogenesis in the fed state [413]. GCs extinguish inflammation and this is in part executed by GR's ability to repress pro-inflammatory gene expression [414]. Numerous transcriptional targets of GR inhibit cytokine release, and GR itself has the capacity to transrepress NF-κB activity [382,383,415] making GR activation a powerful way to resolve inflammation. For that reason, dexamethasone (DEX), a synthetic ligand of GR, has been routinely used as an anti-inflammatory, immunosuppressive agent in the treatment of IBD [416]. Chronic exposure to stress and frequent GC release results in various adverse side effects such as osteoporosis, central adiposity, diabetes, hypertension, dyslipidemia, GI diseases and neurodegeneration [417–420]. Stress is also one of the most significant risk factors for development of irritable bowel syndrome [421–423]. Furthermore, a deficient or blunted HPA axis is commonly observed in the clinic in a wide range of autoimmune and inflammatory diseases [424–426].

In the intestine, GCs impact nutrient absorption by modulating expression of digesting enzymes [427], and enhance glucose uptake by stimulating gene expression of glucose transporters [428,429]. In coordination with the microbiota, they regulate gut ontogeny [427], play a role in the differentiation of the IEC, regulate the expression of tight junction proteins and thus, maintain the intestinal epithelial barrier [430,431]. GR is capable of antagonizing TNF-α-induced increase in MLCK protein expression, a key process mediating the TNF-α increase in intestinal tight junction permeability during inflammation [430]. Thus, GCs released during stress may have a gastroprotective action [432]. It has been shown that creating a lesion in the hypothalamic PVN or administration of antiserum of

ACTH inhibits increases in corticosterone and induces gastric erosions provoked by cold-restraint as well as water and immersion-restraint stress; corticosterone replacement was able to prevent these malfunctions [432].

In the CNS, GR is implicated in both short- and long-term adaptations in response to stressors and participates in brain structural and physiological changes after stress exposure [433–435]. GR regulates the expression of genes related to neuronal and glial metabolism, neuronal plasticity and neurotransmission, and mediates gap junction intercellular communication in neural progenitor cells [436–438]. Stress-activated GR in microglia triggers changes in cell morphology and increases the production and release of inflammatory cytokines, switching from brain surveillance function to eliciting unfavorable effects on neural function and behavior [439–441]. Chronic stress and prolonged GC exposure have profound effects on emotion and cognition. It leads to maladaptive neuronal and glial plasticity, changes brain microglia morphology resulting in neuropsychiatric disorders such as affective, behavioral, and cognitive syndromes including depression, mood imbalance, increased fear conditioning and anxiety [433,441–445]. Adult rats raised by interactive mothers with high licking and grooming behavior, compared animals fed and groomed by less interactive females, show increased hippocampal GR expression, reduced HPA activation and less fear behaviors in response to acute stress [446–448]. Over-activity of the HPA axis is characterized by elevated levels of cortisol and disruption of GCs' negative-feedback and is commonly associated with depression and post-traumatic stress disorder (PTSD) [449,450]. Methylation of the GR gene promoter, which impacts circulating cortisol levels, is negatively associated with severity of PTSD and correlates with specific responses to stress [451]. Moreover, individuals with major mental illness, who often exhibit hypercortisolemia, may have downregulated levels of GR mRNA. For instance, GR mRNA levels are reduced in parts of the cortex of patients suffering from depression, bipolar disorder, and schizophrenia. Furthermore, schizophrenia and bipolar disorder are associated with low GR mRNA levels in parts of the hippocampus [452].

Several studies indicate an impact of stress, GCs and GR on the gut microbiota. Different types of psychological stressors including chronic social defeat, restraint conditions, crowding, heat stress, and acoustic stress can alter the composition of the GI flora [453–458]. Stress induces gut permeability enabling bacteria and bacterial antigens to cross the epithelial barrier, which can activate a mucosal immune response with impact on the microbiota composition [19–21]. Importantly, in lean female mice, stress exposure modifies the microbiota composition to resemble that of obese mice [459]. Maternal separation of rat pups elicits alteration of the fecal microbiota, intestinal dysbiosis, and alters the HPA axis and colonic cholinergic neural regulation [18,456]. Early life stress increases visceral sensation, plasma corticosterone and systemic immune response in the stressed animals after an LPS challenge [18]. Exposure to DEX both acutely (10 days) or chronically (over 4 weeks) in mice leads to substantial shifts in gut microbiota accompanied by a significant downregulation of colonic *mucin 2* gene expression. Importantly, DEX treatment affects mucin expression only in specific-pathogen-free (SPF) but not GF mice. Thus, DEX alone is not sufficient to regulate mucin synthesis in the absence of gut microbes [460]. Moreover, a single high-dose injection of DEX increased the number of ileal anaerobic bacteria, while low-dose GC resulted in an increase in coliform bacteria [461]. These alterations in gut bacteria regulate the inflammatory state in a genetically susceptible mouse model of colitis, demonstrating a gut microbe-mediated mechanism by which GCs exert their anti-inflammatory effects in the colon. Thus, GC signaling partly mediates its effects through gut microbes.

Reciprocally, the gut microbiota also mediates stress responses, which is supported by the fact that an altered gut microbiota can lead to substantial shifts in the HPA axis response to stress [462]. Along a similar line of thought, GF mice present both a reduced anxiety phenotype and disturbed hypothalamic–pituitary–adrenal (HPA) axis [8,41–43]. However, in GF mice a mild restraint stress induces an excessive HPA response and higher plasma ACTH and corticosterone levels compared to the SPF controls, which can be partially reversed by colonizing the GF mice with the flora from SPF

animals or with only *Bifidobacterium infantis* [43]. In contrast, reconstitution with the enteropathogenic *Escherichia coli*, but not with its mutant strain deprived of the translocated intimin receptor gene, enhances the response to stress even further, implying that commensal microbiota can affect the postnatal development of the HPA stress response in mice [43]. In another study using the forced swim test, 28 day long administration of *Lactobacillus rhamnosus* (JB-1) produced animals with lower levels of stress-induced corticosterone and reduced depressive and anxious behavior phenotypes [45]. This outcome was abolished with vagotomy, demonstrating that functional gut to brain direct nerve signaling is necessary for mediating stress response [45]. The HPA axis response to acute stress can also be attenuated by treatment with *Lactobacillus farciminis* [463]. Administration of a probiotic combination of *L. helveticus R0052* and *B. longum R0175* reduced anxiety-like behavior in rats and alleviated psychological distress in volunteers [44]. Moreover, administration of the prebiotics fructooligosaccharide (FOS) and galactooligosaccharide (GOS) abolished the corticosterone response to acute swim stress, attenuated anxiety related behavior in naive mice, and anxiety parameters in chronic social defeat [464]. Delivery of two strains of *Lactobacillus* species to mice pups ameliorated maternal separation-induced gut functional abnormalities and reduced bacterial adhesion and penetration into the colonic mucosa. Moreover, probiotic treatment improved gut dysfunction induced by maternal separation, at least in part by reducing the elevated corticosterone levels and by normalizing the activity of the HPA axis [465]. Thus, adequate stress response of the host depends on microbiota-regulated metabolism of GCs.

3.5.2. Mineralocorticoid Receptor

The MR shows an affinity for MCs like aldosterone, its precursor deoxycorticosterone, as well as for GCs. MCs are a class of steroids produced in the adrenal cortex which mainly influence electrolyte and fluid balance, hemodynamic homeostasis and tissue repair. MR is expressed in many tissues such as the kidney, colon, heart, CNS, adipose tissue, macrophages and sweat glands [466]. In the brain, MR is largely restricted to neurons in limbic areas such as the hippocampus and amygdala [368,467,468]. This contrasts with the GR, which is expressed throughout the brain [368]. The hormones estrogen [469] and progesterone [470], and the nuclear receptors GR, MR, and their MR:GR heterodimer can activate *MR* gene transcription [471]. The promoter of the *MR* gene also contains a noncanonical cAMP-responsive element, which for instance allows GPR48 stimulation of MR expression through the cAMP/PKA pathway [472]. The *MR* gene can generate several transcripts [473], which in humans are derived from two different promoters [471,474]. GR and MR are co-expressed in many types of tissues, often in the same cells, where they interact at the molecular and functional levels, in synergy, but sometimes also in antagonism. GR and MR can coordinate their actions, for example in regulating neuronal Ca^{2+} voltage-gated currents in the hippocampus [475–477]. In preadipocytes, selective MR activation results in the transcription of several genes, including *Pparγ* required for preadipocyte maturation. On the contrary, GR agonists prevent adipogenesis [478,479]. Moreover, in response to inflammation GR often dampens MR's effects. Overstimulation of MR in the heart, vessels, kidneys, and parts of the brain may lead to increased reactive oxygen species, inflammation, and cardiovascular and renal diseases [480]. Thus, balanced MR and GR activities are crucial for adaptation to stimuli and homeostasis [481,482]. The DNA binding domains of MR and GR are nearly identical, and both receptors are capable of binding GREs as well as nGREs [483,484]. Besides competing for the same ligands MR and GR share several co-regulatory proteins required for the initiation of transcription. However, the primary functions of MR and GR and some of their ligands serve different purposes and are regulated very differently [485,486]. A fundamental role of MR includes the regulation of ion and fluid transport in order to sustain osmotic and hemodynamic homeostasis, maintenance of membrane excitability in neurons and muscle cells as well as responses to injury. MR regulates blood pressure, and its inappropriate activation leads to hypertension [487–489]. Treatment with MR antagonists decreases both cardiovascular risk markers and insulin resistance [487–490]. Accordingly, bacterially-derived GC metabolites have been suggested to cause hypertension [360]. Besides acting as

a typical NR and modulating gene expression, MR displays several rapid nongenomic activities which do not require transcription and are mediated by classical cell signaling pathways [491–494]. The types of nongenomic signaling mediated by MR vary between different cells and depend on the activating stimuli. Typically, it includes protein kinase C (PKC), cyclic adenosine 3′,5′-monophosphate (cAMP) and phosphoinositide 3-kinases (PI3K), cumulating with downstream activation of various kinases, ion channels and pumps [491–494]. MR also acts through the EGF–EGFR–MEK1/2–ERK1/2 signaling cascade which influences cell differentiation, proliferation and repair [492,495,496]. In various tissues, nongenomic MR activation leads to intracellular Ca^{2+} flux [497].

MR exhibits different ligand preferences depending on the tissues: aldosterone in the kidney and colon epithelia, and GCs in most parts of the brain. In most tissues at basal levels, GCs favors binding to MR. For instance, in the hippocampus MRs bind GCs with approximately 10-fold higher affinity than its colocalized GR. When GCs levels rise due to stress or circadian cycle GCs also activate GR [366,368,498–500]. Thus, GR is thought to be responsible for the GCs-triggered stress response. However, MR located at the plasma membrane has been shown to also mediate stress level GC effects in a nongenomic manner in the hippocampus [501]. In the brain, GCs are more abundant than aldosterone, thus they constantly occupy MR. GCs are able to passively diffuse across the plasma membrane, and their bioavailability within the cell is controlled by two 11β-hydroxysteroid dehydrogenase enzymes. 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2) converts cortisol and corticosterone to the inactive cortisone, and 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) converts cortisone back to its active form [502,503]. The two 11β-HSD enzymes show cell-specific expression, therefore controlling the level of active GCs and in turn receptor activation. 11β-HSD2 is expressed in aldosterone-sensitive tissues, including kidneys, liver, lungs, colon, salivary glands, H2D2 neurons and placenta, while 11β-HSD1 is highly expressed in key metabolic tissues like liver, adipose tissue, and CNS. Inactivation of GCs by 11β-HSD2 allows binding of aldosterone to the MR within aldosterone target cells, and at the same time, limits activation of the GR in these cells [504–506]. 11β-HSD1 plays an important role in switching between MR-mediated proinflammatory activation of IL-6, TNF-α and NF-κB and GR-triggered suppression of these factors in microglial cells [507]. Thus, this enzyme mediates activation of microglia and may affect the development of neurogenerative diseases. Remarkably, the microbiota is able to produce glycerrhetinic acid-like factors (GALFs), named after glycerrhetinic acid from licorice root, which can inhibit 11β-HSDs activity [360]. Therefore, by modulating the activity of the 11β-HSD enzymes, the microbiota influences whether MR or GR is activated.

Appropriate activation of the MR is essential for normal neuronal differentiation, migration, and function of the developing and adult brain [508–511]. Chronic social stress in adolescent mice evokes a decrease in the mRNA levels of MR and GR in the hippocampus. It also increases adrenal weight, elevates GCs levels, dampens the circadian rhythm and promotes anxiety-related behaviors compared to unstressed mice. The decrease in MR expression and behavioral changes are still detectable a year later, suggesting underlying epigenetic events [512]. Subjects suffering from depression and bipolar disorder display reduced total MR and increased ratio of MR to GR mRNA expression in the prefrontal and anterior cingulate cortex. On the contrary, a decreased MR to GR ratio for both mRNA and receptor is seen in the dorsolateral prefrontal cortex and PVN [513]. Moreover, chronic treatment with corticosterone triggers a depression-like phenotype in mice, however, co-administration of a MR-specific antagonist, spironolactone, mitigates depressive behavior [514]. Both MR and GR participate in corticosteroid-induced direct transcriptional repression of the *5-HT$_{1A}$* gene [483]. Physiological effects of 5-HT$_{1A}$ receptor agonists are attenuated after chronic treatment with GCs [515,516]. Therefore, both receptors influence behavior and impact depression [445,517,518].

The hippocampus, which shows the highest expression of MR in the brain, is the major integrative center for the formation of memories, learning, cognition, and coping with stress. In fact, MR activity is crucial for learning and for forming memories. MR antagonists boost cognition in heart failure patients, sometimes without an actual impact on cardiac function [519] while the decrease in MR

expression in the aged hippocampus positively correlates with age-induced impairments in spatial memory [520]. However, for optimal cognitive performance, balanced activation of both MR and GR is required [521]. Interestingly, therapy with the antidepressant amitriptyline in young rats increases hippocampal MR but not GR expression, and stimulates spatial memory. The same treatment has no effect in aged rats [522]. Furthermore, long-term treatment with amitriptyline in middle-aged rats prevented the prevalence of cognitive impairments and reduced anxiety-related behaviors in aged rats [523]. In contrast, short-term use of MR antagonists in healthy humans has adverse effects on attention, memory, and cognition [524].

In summary, the microbiota modulates levels of GCs thereby affecting activity of GR and MR in multiple organs including the brain (Figure 3).

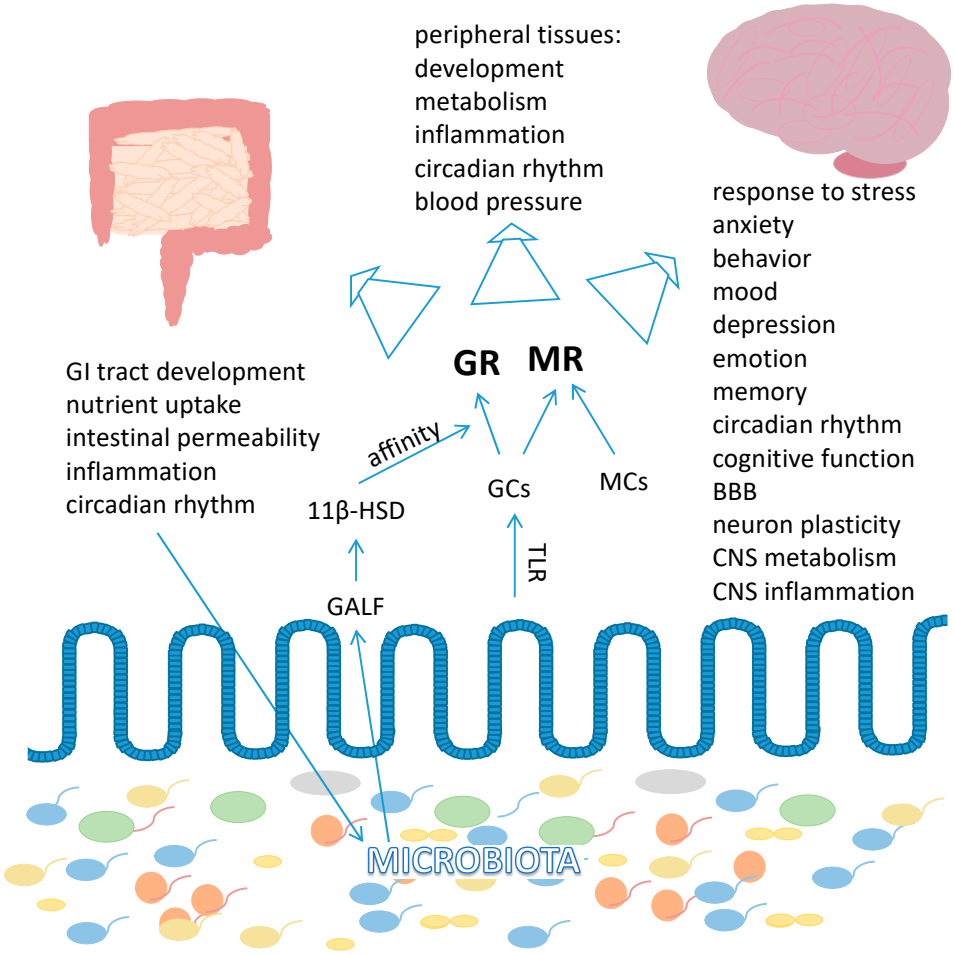

Figure 3. Interaction between glucocorticoid receptor (GR), mineralocorticoid receptor (MR) and microbiota. By regulating the activity of 11β-HSD, bacterial glycerrhetinic acid-like factors (GALFs) modulate GCs availability and GCs affinity towards GR or MR. Additionally, the microbiota regulates circadian production of GCs in the intestine thereby affecting the activity of steroid receptors in multiple tissues.

3.5.3. Estrogen Receptors

Estrogens are primarily produced in the ovaries, adrenal glands and adipose tissue and are C-18 steroid hormones derived from the reduction of C-27 cholesterol. The main forms of endogenous estrogens are estradiol (E2), which is predominant in nonpregnant women prior to menopause; estrone (E1), present after menopause; and estriol (E3), abundant during pregnancy [525]. While passing through the liver E1 and E2 estrogens undergo irreversible hydroxylation at the C-2,

C-4, or C-16 positions of the steroid ring. These modifications produce estrogen metabolites varying in hormone potency and half-life. The types of estrogen and their modifications influence their preference for and capacity to activate different types of estrogen receptors (ERs) [526].

Estrogens mainly play role in reproduction, however, they are also vital modulators of metabolism and behavior. They protect against high-fat diet induced insulin resistance and glucose intolerance in mice [527]. Lower levels of estrogens in postmenopausal women [528] or in ovariectomized animals are associated with obesity [529], while estradiol-17β replacement in ovariectomized mice prevents weight gain by diminishing food intake and stimulating energy expenditure [529]. Accordingly, hormone replacement therapy in postmenopausal women reverses the progression of obesity and metabolic dysfunctions [530]. Importantly, estrogen levels strongly impact gut microbiota composition and microbiota affects body weight. In men and postmenopausal women, levels of total urinary estrogens correlate to richness and α diversity of fecal microbiota [531,532]. Ovariectomy in adult mice diminishes gut microbiota richness [533]. In rats, neonatal androgenization or adult ovariectomy causes shifts in the relative abundances of the two major phyla causing a higher *Firmicutes* to *Bacteroidetes* ratio [533]. In humans, similar gender-dependent differences were observed. Estrogens are strongly and significantly associated with the fecal *Clostridia* taxa, including non-*Clostridiales* and three genera in the *Ruminococcaceae* family [531], while men have higher levels of *Bacteroidetes* and *Prevotella* than women [534,535]. In mice, sex differences in gut microbiota are decreased after castration of male mice [536]. Stunningly, hormonal changes caused by early androgenisation or ovariectomy impact the microbial flora more strongly than nutritional changes from chow to a high fat diet [533], suggesting a decisive role for gonadal hormone levels in the modulation of GI flora.

A cluster of bacteria, referred to as "estrobolome" due to its capacity to metabolize estrogens, can significantly influence the host's estrogen levels [537]. The series of reductive reactions leading to the synthesis of estrogens from cholesterol is partly catalyzed by hydroxysteroid dehydrogenases (HSD), a group of alcohol oxidoreductases. Bioinformatic annotation of HSD in all entirely sequenced bacterial genomes has proven that HSDs are found in a wide variety of microorganisms including bacteria and archaea. A large number of HSD-expressing bacteria participate in the normal human gut microbiota [538].

After circulation in the blood, estrogens and their metabolites are directed to the liver where they are conjugated through glucuronidation or sulfonation which facilitates their excretion in the bile, urine and feces [539]. β-glucuronidases and β-glucosidases, expressed by several bacterial strains, are capable of deconjugating estrogen which can then be reabsorbed by the intestine and reenter the host's estrogen pool [540,541]. The activity of fecal bacterial β-glucuronidase activity, just like the intestinal flora composition, can be modulated by diet [542–544]. In rats, a decrease in fecal β-glucuronidase enzyme activity was observed after antibiotics administration [545]. In line with this observation, antibiotic therapy results in significant increases in fecal conjugated estrogens and a reduction in urinary estrogen in men and women [546–548]. More than half of the low G + C% gram-positive *Firmicutes*, which are a dominant bacterial group within the human large intestine [549], harbor β-glucosidase activity [550]. Most of *Bacteroides* spp. carry high β-glucuronidase and β-glucosidase activity, while the majority of *Bifidobacterium* spp. show only β-glucuronidase activity. The highest β-glucuronidase and β-glucosidase activities in feces correlate with the occurrence of *Clostridium* spp. [540,550,551]. Similarly, *Peptococcus niger* by means of sulfatase activity can deconjugate estrogen sulfate metabolites [552]. Furthermore, the gut microbiota is able to metabolize estrogen-like compounds from nutrition. For instance, daidzein found in soy can be metabolized to O-desmethylangolesin (ODMA) and S-equol [553], which are structurally similar to estrogen and can activate ER [554,555]. It is noteworthy that individuals harboring a gut flora capable of producing ODMA, but not S-equol, are more likely to be obese [553]. Importantly, several epidemiologic studies have suggested a possible association of antibiotic use and breast cancer risk which may be a consequence of disturbed estrogen metabolism [556,557].

Microbiota-derived estrogen may influence the host's fertility. In GF mice, reproduction capacity is lower than in SPF mice. Inoculation of GF mice with *B. distasonis* and *C. perfringens* induces significant increase in sperm motility in male mice while in females it results in the normalization of the estrous cycle, and rises the copulation and fertilized egg implantation rates. On the contrary, the reproduction rate of mice carrying only the single *Bacillus subtilis* strain is comparable to GF mice, underscoring the importance for hormonal homeostasis of selected bacterial strains in the gut [558].

Estrogen exerts its activity via the estrogen receptor α (ERα, NR3A1) and β (ERβ, NR3A2) [559,560]. ERα and ERβ are highly homologous, particularly in the DNA binding domains (95%) and the ligand binding domain (55%), and show affinity for the same estrogen response elements (ERE) in DNA [560]. Although ERα and ERβ share similar ligand binding domains, ERβ possesses a relative binding affinity for several steroid hormones that differs from that of ERα [561]. ERα and ERβ are expressed in multiple organs [562] including all parts of the GI tract [563–566], but their expression levels differs in various tissues. For instance, ERα is the predominant isotype in the breast and uterus, whereas ERβ is expressed at higher levels in the urogenital tract, endothelial cells and the CNS [562,567]. ERα and ERβ are present throughout the rostral–caudal extent of the brain and spinal cord and their expression overlaps in most of the CNS with a few exceptions. For instance, although both receptors are expressed by neurons in the arcuate nucleus and hippocampus, ERα is more abundant in the arcuate nucleus, and ERβ is more prevalent in the hippocampus [568–572]. Importantly, ERβ mediates brain development by regulating neural progenitor cell proliferation [573] and stem cell differentiation into dopamine neurons [574].

ERα, but not ERβ, is vital to reproductive function and regulation of the preovulatory surge of luteinizing hormone (LH) in response to rising levels of estrogen [575–577]. However, ERβ may be involved in mediating the negative feedback control of anterior pituitary LH secretion, a process mainly governed by ERα [578]. Moreover, ERα-null female mice are deficient in sexual behavioral interactions, they are more aggressive towards other females and show reduced levels of parental behavior towards newborn pups [575]. Thus, ERα regulates reproduction not only at the physiological, but also behavioral level.

The effects of estrogens on energy balance are primarily mediated by ERα, as women or female mice with mutations in the ERα gene display hyperadiposity [579,580]. Importantly, estrogen levels directly affect nutrient uptake from the intestine [581,582]. Female mice lacking ERα in hypothalamic steroidogenic factor-1 (SF1) neurons are characterized by hypometabolism and abdominal obesity, but not hyperphagia. In contrast, loss of ERα from the hypothalamic POMC neurons leads to hyperphagia, without directly influencing energy expenditure or fat distribution [583]. Thus, estrogens act on distinct hypothalamic ERα neurons to regulate different aspects of energy homeostasis and reproduction.

While ERα is essential for reproductive neuroendocrine function, ERβ seems more important for emotional behavior. ERβ-null mice show increases of 5-HT_{1A} receptor expression in the medial amygdala as well as lower serotonin and dopamine levels in several brain regions [584,585]. Accordingly, E2, acting via ERβ located in 5-HT cell bodies of the dorsal raphe nucleus, induces expression of tryptophan hydroxylase which is involved in the synthesis of 5-HT [586]. As a result, mice and rats treated with E2 or selective ERβ agonists and subsequently submitted to the forced swim test, spend less time immobile and struggle longer than non-treated controls, which is interpreted as a less depressive-like behavior [587,588]. This effect is not observed in ERβ-null mice [587]. Selective agonists of ERβ exert potent anxiolytic activity in rats [589,590], whereas ERβ-null mice show increased anxiety accompanied by reduced threshold for the induction of synaptic plasticity in the basolateral amygdala [584,585]. In elevated plus maze and open field tests for anxiety-like behaviors, ERβ-null mice show increased anxiety relative to their wild-type counterparts. Importantly, this phenotype of the ERβ-null mice is present only in females, indicating a specific gender-dependent sensitivity to hormonal changes expressed in behavior [584,585]. ERβ may exert its impact on behavior via the HPA axis [591] and other behavior-related hormones as it represses neuronal vasopressin [592],

CRH [593] and corticosterone [590]. Notably, GCs are transported in the blood predominantly bound to corticosteroid-binding globulin (CBG), also known as transcortin, which serves as a regulator of the biological availability of GCs. CBG is produced by the liver, and interestingly, it is stimulated by estrogens, which is reflected as higher levels of total circulating corticosterone in females compared to males [594]. Importantly, the sex hormones estrogen and progesterone influence the expression of MR [469,470] and the ER inhibits the transactivational effects of the MR in several cell types [595]. In addition to MCs and GCs, progesterone is a competitive MR antagonist with a similar affinity for the MR as aldosterone [596]. Moreover, MR mRNA levels in the human hippocampus show higher concentrations in women compared to men [597]. The hormonal differences associated with MR correlate with occurrence of cardiovascular diseases in premenopausal woman. Consistently, sex differences exist in the cortisol stress response [598], in response to parental separation of pups [599], in hippocampal MR and GR expression after exposure to stress of adults rats [600,601] and in the prevalence of stress-related psychiatric disorders [602,603]. On the contrary, DEX-treated female rats increase ERβ expression in the hypothalamic PVN and supraoptic nuclei (SON) [604], whereas adrenalectomy reduces ERβ mRNA expression in the PVN, and corticosterone replacement fully reverses this effect in a dose-dependent fashion [605]. Thus, ERβ mediates and interacts with the HPA axis.

In contrast, treatment with the ERα agonist propylpyrazoletriol (PPT) was anxiogenic in the elevated plus maze test and, in a consistent manner, stimulated corticosterone stress hormone response [590,593]. These results provide an explanation to the fact that estrogen has both anxiogenic and anxiolytic effects [606,607].

Considering the vital contribution of estrogens to the regulation of fertility, metabolism and behavior described above, the regulation of estrogen bioavailability by the microbiota impacts essential functions in the host's life.

3.6. Thyroid Hormone Receptors

An essential component of thyroid hormones (TH), iodide is actively transported and concentrated in the thyroid gland and incorporated in THs. Thyroid cells combine iodine and the amino acid tyrosine to make T_3 and T_4 [608–611]. Thyroxine (T_4) contains four iodine atoms and the more potent triiodothyronine (T_3) has three of them. T_4 is the prevalent form of released THs and deiodination of its outer ring by enzymes iodothyronine deiodinases yields T_3. The deiodinases are selenoproteins expressed in various tissues including the GI tract which regulate the intracellular biological activity of THs [612–615]. Thus, deficiency of deiodinases can mimic hypothyroidism.

TH secretion is regulated by a negative feedback system involving the hypothalamus, the pituitary gland and the thyroid gland. Thyrotropin releasing hormone (TRH) is synthetized in the hypothalamus and when released it is transported in the circulation and binds to receptors of the pituitary thyrotropes. The pituitary then secretes thyroid stimulating hormone (TSH) which promotes TH release from the thyroid gland. Both TRH and TSH secretions are negatively regulated by TH. Also, somatostatin and dopamine inhibit TSH release [616,617]. Importantly, both of these factors can be produced by microbiota [35,48,49].

THs serve as ligands for the thyroid hormone receptors α (TRα, NR1A1) and β (TRβ, NR1A2), which occur in several forms. TR-α1 is widely expressed with high levels in cardiac and skeletal muscles. In the brain its highest levels are in the olfactory bulb, hippocampus and parts of cerebellar cortex. TR-α2 is most abundant in the brain but it is the only TR form that is not capable of binding thyroid hormone. TR-β1 is present mainly in brain, liver and kidney and TR-β2 is limited to brain with high levels in the hypothalamic PVN and anterior pituitary [618,619]. TR can bind to DNA whether or not it is activated by appropriate ligands. In the unliganded inactivated from it recruits corepressors thereby inhibiting gene expression. Upon ligand binding, the TR changes conformation facilitating dissociation of the corepressors and the recruitment of coactivators resulting in the stimulation of target gene promoters and gene transcription [620]. TRs also exerts nongenomic actions [621].

T_3 increases cardiac output and heart rate, lung ventilation, basal metabolic rate, catabolism of proteins and carbohydrates as well as growth and brain development. In the brain, THs promote a wide range of developmental processes including myelination, neuronal migration as well as neuronal and ganglion cell differentiation [611,619]. THs also affect mood and behavior [622]. Among target genes in the brain TH regulates genes coding for brain myelin basic protein [623,624], BDNF [625], glutamine synthase [626], prostaglandin D2 synthase [627], adhesion molecules, matrix proteins, factors affecting neuronal migration and apoptosis, nerve metabolism and signal transduction [628–630]. Both TH deficiency and excessive production lead to metabolic and neuronal malfunctions. Hyperthyroidism is characterized by increased levels of free circulating TH, weight loss, frequent bowel movements and associated diarrhea, weakness, tremors, difficulty to sleep, heat intolerance, increased heartbeat, anxiety, and memory problems. Hypothyroidism is associated with weight gain, exhaustion, constipation, indigestion, depression, anxiety, psychosis, general pains and fertility problems in females [619,631–633]. Hypothyroidism affects brain development and may cause neurological defects including diminished neuron development in hippocampus, cerebral cortex, visual and auditory cortex [628,634,635]. Hypothyroidism-caused developmental malfunctions can be reversed if THs are administrated within 2 weeks after birth [628]. On the contrary, absence of congenital hypothyroidism treatment in infants leads to a profound brain development delay accompanied by mental retardation. Interestingly, hypothyroid patients show lower amounts of gut *Bifidobacterium* and *Lactobacilli* while having more *Enterococci* than healthy subjects [636]. Additionally, patients with a history of hypothyroidism show more prevalent occurrence of small intestine bacterial overgrowth (SIBO) which may be reversed by antibiotic treatment [637].

Hypothyroidism may be due to genetic factors or dietary iodine deficiency. Iodine concentration in the thyroid gland as well as in peripheral tissues largely depends on ionic pumps and transporters, the efficiency of which is modulated by iodothyronine deiodinases as well as the availability of iodine and selenium. An inability to synthesize TH results in a decrease of the negative feedback to hypothalamus, which stimulates TSH production leading to enlargement of thyroid gland, a condition named goiter. An enlarged thyroid gland enhances its ability to trap iodine [638–640].

The amount of exchangeable T_3 and T_4 in the intestine constitutes the second largest reservoir of TH after the thyroid gland, before the liver and kidneys [641]. Short gut syndrome and bariatric surgery are both associated with reduced intestinal nutrient uptake and malnourishment, which do not influence iodine levels [642,643]. On the contrary, modulation of rat microbiota by kanamycin reduces iodine uptake [644] implying that the gut flora constitutes the functional component of the GI tract responsible for iodine absorption. Moreover, the microbiota in the small intestine, cecum, colon and feces of rats reversibly binds T_3 and T_4 and this capacity is abolished by antibiotic treatment [645,646]. Ex vivo studies show that *Escherichia coli*, one of major gut colonizers, is capable of binding T_3 and T_4 [647]. Thus, gut flora could serve as a reservoir, retaining and releasing TH.

Selenium is an essential microelement required for the synthesis and bioactivity of selenoproteins, including deiodinases. Consequently, this microelement affects the activity of TH. Selenium is absorbed in the duodenum and caecum [648] and in the body is most highly concentrated in the thyroid gland [649]. Gut bacteria also require selenium and when it is not taken up by the host, colonic bacteria utilize it [650]. Upon selenium shortage, the microbiota gets to the point of competing with the host for selenium [651], which may result in reduced expression of selenoproteins in the host [652] and the microbiota may inhibit the enzymatic activity of deiodinases in the cecum and colon walls [653]. Selenium supplementation results in increased diversity of gut bacterial population [652] and enhanced colonic and rectal fermentation [654] as multiple microbes are capable of producing their own selenoproteins [655–658].

THs are inactivated mainly in the liver by conjugation. Attached sulfate and glucuronic acid moieties enable secretion of the conjugated hormones in bile and decrease their reabsorption from the intestine. Moreover, sulfation facilitates irreversible deiodination and catabolism of THs [659]. However, glucuronidated and sulfated THs can be hydrolyzed to active precursors in the GI tract

and various other tissues. Thus, conjugated THs can serve as a reservoir for active hormones. In rats, but not humans, stimulation of glucuronidation by drugs and toxins may results in a drop in T_4 and T_3 levels provoking elevated TSH secretion and resulting in goiter formation [638,660,661]. Incubation of various TH sulfate conjugates with human or rat feces results in complete hydrolysis of the conjugates. However, preheated fecal suspensions and supernatants of centrifuged fecal solution do not affect sulfation of TH. Similarly, fecal suspension obtained from GF or ampicillin-treated rats showed drastically reduced deconjugation capacity [662–664]. Consequently, in GF mice the enterohepatic cycle of TH including intestinal deconjugation of T_3 secreted in bile and its reabsorption to circulation is abolished [665]. Deconjugation activity relies on the presence of obligate anaerobic intestinal bacteria. Bacterial strains isolated from human feces, including *Peptostreptococcus productus*, possess sulfatase activity [662–664].

The bacterial signaling that influences TH turnover and LPS which triggers septic shock also promotes non-thyroidal illness syndrome. Higher doses of LPS in mice decrease the levels of liver deiodinase mRNA, pituitary TR mRNA and protein, and reduces the amount of TSH receptor mRNA in the thyroid gland [666]. In pigs, LPS lowers TH levels in serum and most tissues. Moreover, it decreases the expression of deiodinases in the liver and kidneys as well as deiodinases activity in kidneys. LPS administration results in lowered mRNA levels of TRβ in the frontal lobe, adrenal glands and kidney cortex [667]. Thus, bacterial LPS is capable of affecting TH signaling on multiple levels in the whole organism, including in the brain.

Patients suffering from celiac disease, which is generally accompanied by GI inflammation and abnormal microbiota, show malabsorption of orally delivered T_4 and in case of Hashimoto thyroiditis require higher doses of the T_4 drugs [668]. Approximately one third of patients with autoimmune thyroid disease show also symptoms of atrophic gastritis [669]. Furthermore, 40% of Hashimoto thyroiditis patients exhibit lymphocytic colitis [670]. Rarefication and partial disappearance of microvilli, spaces between microvilli and thickening of microvilli were increased in intestinal mucosal biopsies from autoimmune thyroiditis patients. The patients also showed increased mucosal permeability [671]. Thus the host's TH affects gut health and therefore also the gut flora. TH can also affect the bacteria population by influencing the number of parietal cells in the gastric mucosa, the secretion of pepsinogen and the basal acidity in the stomach [672,673]. Thereby in the stomach, TH increases the efficiency of killing bacteria taken up with the food, reducing the colonization of more distal parts of the GI tract by these foodborne microorganisms.

The direct connection of enteric bacteria and TR in the context of the gut–brain axis has not been addressed so far. However as seen above, the importance of TR in brain development and proper functioning and the crucial impact of the microbiota on TR ligands availability, provide strong support for a GI tract–CNS TR-dependent signaling.

4. Conclusions and Future Directions

As presented in this review, there are multiple studies proving the connection between a healthy gut and a healthy brain. NRs are key players in regulating virtually every process necessary for the survival and health of a living organism. By influencing NRs, gut flora participates in the regulatory roles of the nuclear receptors (Figure 4). Via signaling to the brain, the microbiota regulates metabolism, CNS development, inflammation as well as mood and behavior. Notably, it also impacts reproductive behavior and, therefore, contributes to species survival. Importantly, the human host has the capacity to voluntarily influence and improve its own microbiota by the power of nutritional or probiotic interventions. Thus, nutritional approaches, combined with physical exercise, aiming at providing or sustaining the production of NR ligands and increasing the microbiota diversity should appear as a common sense approach to promote a physically and physiologically healthy life.

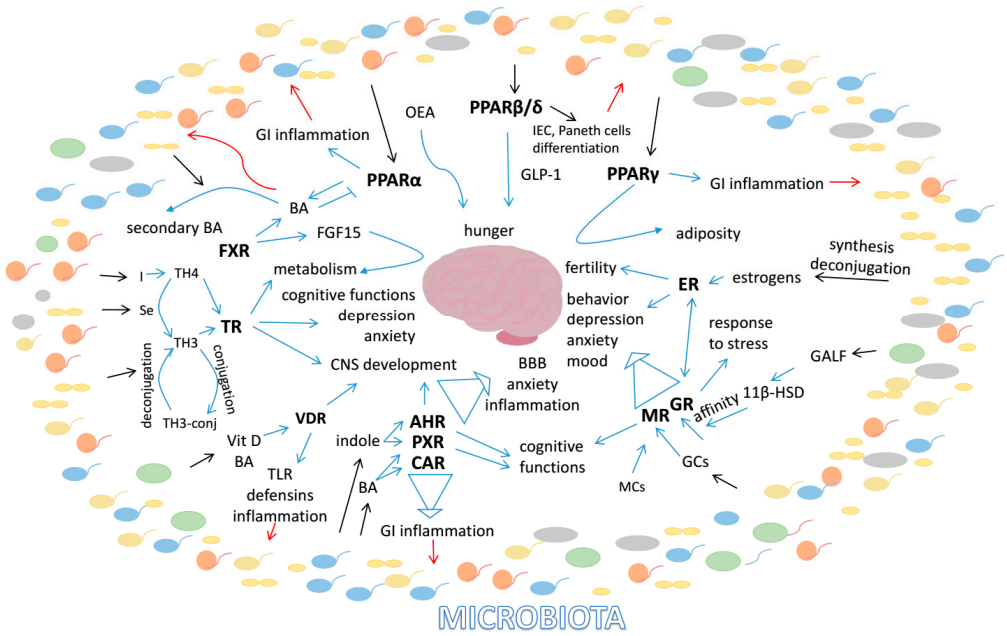

Figure 4. Summary of the interactions of NRs with enteric microbiota and the brain. Broad blue arrows indicate the involvement of groups of NRs (AHR/PXR/CAR; MR/GR), narrow blue arrows picture single factor actions. Black lines illustrate bacteria-born signals and red arrows specify impacts on the microbiota.

Multiple NRs have been proven to interact with the microbiota and/or to play a role in the brain. However, a full picture of the involvement of NRs in the gut–brain axis is still missing. Interestingly, there is one exception. The RAR-related orphan receptor (ROR) is involved in cerebellum development [674]. Additionally, the RORγ subtype is considered to be a master regulator of lineage specification of a subset of $CD4^+$ T helper cells (T(H)17) playing a role in the development of autoimmune diseases [675]. Importantly, microbes induce Th17 cells via RORγ, which results in activation of sensory neurons [676]. Evidence for such a direct regulation of the nervous system by bacteria has been rarely found so far. Therefore, more research is needed to fully unveil the great potential of NRs in regulating the enteric microbiota–gut–brain axis and to learn how we could benefit from modulating their activity by pharmacological or nutritional interventions.

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