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REVIEW

Endocrine Disruptors and Gut Microbiome Interactions

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Summary

Anthropogenic environmental pollutants affect many physiological, biochemical, and endocrine actions as reproduction, metabolism, immunity, behavior and as such can interfere with any aspect of hormone action. Microbiota and their genes, microbiome, a large body of microorganisms, first of all bacteria and co-existing in the host´s gut, are now believed to be autonomous endocrine organ, participating at overall endocrine, neuroendocrine and immunoendocrine regulations. While an extensive literature is available on the physiological and pathological aspects of both players, information about their mutual relationships is scarce. In the review we attempted to show various examples where both, endocrine disruptors and microbiota are meeting and can act cooperatively or in opposition and to show the mechanism, if known, staying behind these actions.

Key words

Endocrine disruptors • Gut microbiome • Reproduction • Metabolism • Immunity • Mental health

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Introduction

Environmental factors known as endocrine disruptors affect many physiological, biochemical, and endocrine actions as reproduction, metabolism, immunity, behavior and as such can interfere with any aspect of hormonal action. For reviews see the particular chapters below. Several reports addressing this issue were reported also in this journal (Müllerová and Kopecký 2007, Vitku *et al.* 2015, Kolatorova *et al*. 2017, Kolatorova *et al*. 2018a, Kolatorova *et al.* 2018b, Vitku *et al.* 2018, Jambor *et al*. 2019).

Gut microbiota participates at many of these processes and is often considered as a further autonomous endocrine organ. Gut microbiota, first of all bacteria, produce a number of biologically active molecules which *via* signaling pathways, influence physiological functions, while in turn, the host affects considerably microbiome composition and activities. Through permeable gut wall endocrine disruptors from circulation enter directly the intestinal milieu or, by interaction with enteric nervous system, may affect composition and functions of gut microbiome. Out of thousands reports and reviews let us mention at least Cresci and Bawden 2015, Heintz-Buschart and Wilmes 2018, Salvucci 2019.

Gut dysbiosis, as a state consisting of prevalence of non-commensal bacteria might in turn result in many disorders such as obesity, diabetes, gastrointestinal, endocrine, immunological, and neurobehavioral diseases (Rosenfeld 2017). Such host diseases can originate due to shifts in microbiota composition favoring more pathogenic species and phyla.

Both gut microbiota and endocrine disruptors may affect the same physiological and pathological processes mentioned above, though often in a different way. Table 1 shows the number of references collected on PubMed to the date 30th September 2019, concerning the effects of gut microbiota at one side, and endocrine disruptors at another, on reproduction, immunity, diabetes plus related disorders, and mental diseases. The key words in the table were used for the search.

In this overview we attempted to show the main ways how various endocrine disruptors influence gut microbiome richness and composition with consequent pathological outcomes.

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Table 1. Number of papers addressing the effect of endocrine disruptors on microbiome composition and *vice versa* and papers dealing with relation(ship) of gut microbiota to reproduction, diabetes and related disorders, immunity and mental/or brain disorders (left column) and analogically their relation to endocrine disruptors (right column).

Gut microbiota	14	Endocrine disruptors
655	Reproduction	3655
4575	Immunity	289
1501	Diabetes, obesity, metabolic syndrome	307
218	Mental disorders or brain	711

Studies on the effect of endocrine disruptors on the composition and function of microbiota

From the data of Table 1 it is evident that there are only few reports concerning the effect of endocrine disruptors on host microbiome. Several reviews have been published recently: Velmurugan *et al*. 2017, Rosenfeld 2017, Feng *et al*. 2018, Evariste *et al*. 2019.

The first review from Indian authors (Velmurugan *et al.* 2017) focused on the role of gut microbiota in glucose dysregulation induced by individual classes of endocrine disruptors (EDs) from plastics, pesticides, synthetic fertilizers, electronic waste, and food additives. They included bisphenols, dioxins, phthalates, organochlorines, organophosphates, fungicides, polychlorinated biphenyls and polychlorinated dibenzofurans. They have shown increasing incidence of diabetes characterized by hyperglycemia, glucose intolerance and insulin resistance, hand in hand with amount of produced EDs-containing waste pollutants, many of which act as diabetogenes. The increase of diabetes prevalence, at least in India, did not correlate with common risk diabetic factors – obesity, hypertension, hypercholesterolemia or smoking, emphasizing the role of the latter chemicals. At the same time hyperglycemia was associated with changes of microbiota composition, preferring the non-commensal ones, on the detriment of beneficial phyla such as Bacilli (e.g. *Lactobacillus), Bacteroidetes, Proteobacteria,* and *Actinobacteria*. The ratio *Bacteroidetes/Firmicutes* correlated with plasma glucose concentration. Microbiota are capable to ferment undigested carbohydrates, fiber, and other dietary and xenobiotic compounds to produce short-chain fatty acids (SCFAs), which, through their ubiquitous receptors, play an important role in host glucose metabolism. EDs interfere with the latter gut microbial processes, consisting in induction of specific microbial genes, enzymes, and metabolites. Microbiota, in turn may transform EDs into new compounds which may differ in their biological activity. A typical example is DDT, which is dechlorinated by gut microbiota to DDD.

The mutual relationship between environmental exposure to EDs, host status, especially as concerns the pathophysiological situations mentioned in Table 1, and gut microbiome changes was comprehensively reviewed by Rosenfeld (2017). The author collected original papers published until 2017, all of which dealt with animal models. In summary, EDs change hormonal function either by affection of hormonal biosynthesis or by interaction with hormonal receptors. EDs affect production of various steroid and peptide hormones as estrogens, testosterone, glucocorticoids, insulin and likely other hormones. Altered hormonal milieu may result in changes of gut microbiota and dysbiosis. EDs can impact gut microbiota also directly, especially during the perinatal period, when microbes begin to colonize the gut. It is likely that certain bacteria are differently vulnerable to environmental chemical exposures. An example is the effect of bisphenol A (BPA) the exposure to which led to microbiota changes similar to those elicited by high fat diet. Generally, dysbiosis is characterized by altered production of signal molecules by microbiota as already mentioned SCFA, neurotransmitters, cytokines and last but not least hormones, some of which are further metabolized (example: β-glucuronidase).

The review of Chinese authors (Feng *et al.* 2018) collected the recent data on the impact of selected environmental contaminants as heavy metals, antibiotics and pesticides on gut microbiome composition and its influence on host physiology. It included organophosphate insecticides chloropyrifos, malathion, diazinon and glyphosate, organochlorine pesticides as permethrin and pentachlorophenol, all acting as EDs. They brought evidence that several commensal bacteria as *Lactobacilli* can diminish the accumulation and toxicity of pesticides in animal tissues by inhibiting intestinal absorption of contaminants and promoting tight junctions which constitute the intestinal barrier. Microbiota is also capable to transform several EDs to metabolites differing in their toxic properties as demonstrated on organophosphate insecticide chloropyrifos. The second part is focused on the effects of probiotics on improving

the microbiome composition, following exposure to above mentioned environmental agents. In summary, probiotics as e.g. *Lactobacilli* protect against EDs induced oxidative stress and consequent cellular damage, contribute to integrity of intestinal barrier, resulting in EDs absorption and stimulate host's immunity.

Recent review from France (Evariste *et al.* 2019) focused on aquatic organisms. It shows how various environmental contaminants contribute to modifications of gut bacterial communities and dysbiosis. All the cited studies of the microbiota changes were based on 16S rRNA sequencing. Besides heavy metals, antibiotics, nanoparticles and personal health products it included a pesticide pentachlorophenol, a fungicide imazalil (enilconazol), a herbicide atrazine, an antimicrobial agent triclosan, groups of polychlorinated biphenyls and polybrominated diphenyl ethers and BPA. In most but not all instances exposure to the pollutants led to an increase of non-commensal microbiota, on the detriment of beneficial bacterial phyla as characterized e.g. by the *Firmicutes/Bacteroidetes* ratio. From this point of view, rather surprising is the effect BPA, which at least in zebra fish decreased proportion of *Bacteroidetes* and increased proportion of phylum CKC4. The review also summarizes the literature on abilities of microbiota to biotransformation of individual classes of environmental pollutants and thus to modulate their toxicity.

Table 2 summarizes the recent studies on environmental chemical pollutants and their coincident effects on host physiology and gut microbiota/ microbiome changes. Most of them act also as classical endocrine disruptors, though the cited papers can deal with other impacts on host physiology. As may be seen, most original papers dealt with bisphenol A, first of all thanks to its effects as an environmental estrogen, but impact of its exposure is not limited only to reproduction. Some of these papers are mentioned in the above cited reviews (Velmurugan *et al*. 2017, Rosenfeld 2017, Feng *et al.* 2018, Evariste *et al.* 2019).

On the other hand there are many examples where the effects of EDs and gut microbiota are meeting, as we attempt to show in the following text.

Endocrine disruptors, gut microbiota, and reproduction

EDs affect male as well as female reproduction. The last decades monitor the decrease of sperm count and quality in men as well as in wild life, which are related to exposure to various anthropogenic pollutants (Mauduit *et al*. 2006, Di Nisio and Foresta 2019). EDs represent the risk for female health and reproduction as well, including harmful transgeneration effects on offsprings (Waring and Harris 2011). Extensive literature is available on this topic (Table 1) including a number of reviews and metaanalyses (Gore *et al*. 2015, Kabir *et al*. 2015, Sifakis *et al.* 2017). In summary, EDs in males influence spermatogenesis and semen quality, in females conception, pregnancy and delivery. La Merrill *et al*. (2020) defined the main levels (named as key factors), where EDs interfere with hormone action, resulting in reproduction disorders: EDs can interact with hormone receptor either as activator or antagonist and even can alter hormone receptor expression. EDs can alter hormone elicited signal transduction, including changes in protein or RNA expression and post-translational modifications in hormone-responsive cells. EDs can induce epigenetic modifications in hormone-producing or hormone-responsive cells. EDs can alter hormone synthesis and thus change hormone distribution or circulating hormone level. This concerns especially hormonal steroids. EDs can alter hormone transport across cell membranes by affecting their permeability. EDs are able to affect hormone metabolism or clearance, resulting in further changes of their circulating levels. Below are shown typical examples where EDs and gut microbiota may act in common either as agonist or antagonist.

The main effect of EDs on male reproduction disorders, such as impaired spermatogenesis and abnormal sperm production, consists in disruption of testicular steroidogenesis in Leydig cells (Vitku *et al.* 2016, Jambor *et al*. 2019). Wan *et al.* (2013) described the sites of hormonal events leading to androgen production, at which EDs can execute their effects. Both expression of key players in hormone signaling and inhibition of mitochondrial enzymes of androgen biosynthesis may occur. Certain fecal microbiota are capable not only to metabolize, but also to synthesize steroid hormones. The historical view on enzymology of steroid transformations carried out by microbiota can be found in the paper of Devendran *et al*. (2018). So far only little information is available on association between EDs-caused impaired steroidogenesis and gut microbiota (Ding *et al*. 2020). This issue, especially the possible beneficial counteracting effect of commensal bacteria on concrete EDs-induced errors in androgen production, need further investigation.

Table 2. Survey of studies on the effect of endocrine disrupting chemical on host physiology and gut microbiome composition and function.

ED (Chemical group)	Type/Use	Model	Main effects on host physiology and endocrine disrupting activities	Effect on gut microbiome composition and function	Reference *
Bisphenol A (bisphenols, diphenyl methane derivatives)	Broad use in plastics and other anthropogenic materials	Female mice	Estrogenic effects on parents and offsprings	Changes of microbiota in the direction to female sex	Javurek *et al.* 2016 R
Bisphenol A (bisphenols)	See above	Mice	Classical endocrine disruptor affecting both male and female reproduction	Overabundance of *Protobacteria* similar as at high fat diet	Lai *et al.* 2016 R, V
Bisphenol A (bisphenols)	See above	Male zebrafish	Affects male reproduction as an environmental estrogen	Altered the intestinal microbial composition with the abundance of the phylum *CKC4*	Liu *et al.* 2016 R, E
Bisphenol A (bisphenols)	See above	Male and female dogs	Changes of hematological and plasma chemical parameters including cortisol levels	Negative correlation of relative abundant phyla *Bacteroides* and *Flexispiraphyla* with BTA levels; Increased plasma bicarbonate concentrations associated with fecal microbiota alterations	Koestel *et al.* 2017 R
Bisphenol A (bisphenols)	See above	Rabbit offsprings	Perinatal BPA exposure-induced intestinal (and liver) inflammation in offspring and increased gut permeability	Bacterial dysbiosis, especially reduction in the relative abundances of phyla *Oscillospira* and *Ruminococcaceae* producing short-chain fatty acids	Reddivari *et al.* 2017
Carbemazin (benzimidazol derivative)	Fungicide	Mice	Affects male fertility by destruction of testicles, inflammation, dyslipidemia	Reduction of GM richness and diversity. Relative abundance of *Firmicutes, Protobacteria and Actinobacteria, decrease of Bacteriodetes*	Jin *et al.* 2015 V
Chrysene and polycyclic aromatic hydrocarbons (PAHs)	Environmental pollutants from soil and air	Day care children from urban areas	Endocrine signaling disruptors. Peroxisome proliferator-activated receptor and adipocytokine signaling pathway decreased with higher PAH concentration in the air	Soil PAH contamination was associated with altered *Actinobacteria*, *Bacteoridetes* and *Proteobacteria* communities on children's skin	Roslund *et al.* 2019

Diazinone (organophosphate) Triclosan and their mixture	Insecticide antibacterials used in personal health products	Male and female mice	Acetylcholinesterase inhibitor, neurotoxicity	Changes of the gut microbiome in a sex-specific manner, with stronger responses in male mice.	Gao *et al.* 2017 F, V
2,3,7,8-Dibenzofuran (Chlorinated dioxins and furans)	Ubiquitous persistent organic pollutant	Mice	Affects glycoregulation, hepatic lipogenesis, promotes inflammation	Dietary chlorinated dioxins and furans altered the gut microbiota by shifting the ratio of *Firmicutes* to *Bacteroidetes*	Zhang *et al.* 2015 V
p, p'-dichloro-diphenyldichloro-ethylene, β-hexa-chlorocyclohexane	Organochlorine pesticides	Mice	Changes in bile acid composition due to expression of genes encoding for principle enzymes, reduced reabsorption and hydrophobicity	Increase of phyla *Firmicutes* and *Proteobacteria* but decrease of *Bacteroidetes, Verrucomicrobia, Actinobacteria and Candidatus Saccharibacteria*	Liu *et al.* 2017 F
Diethylphtalate Methylparaben Triclosan and their mixture	Plasticizers, conservants and antibacterials used in personal health products	Female rats	Broad effects on female as well as male reproduction, interaction with steroid hormone receptors	Relative increase of *Bacteriodes* phyla and decrease of *Firmicutes* following exposure to all these EDs	Hu *et al.* 2016 R
Doxycycline (tetracycline antibiotics)	Antibacterial and antiparasitic agent	Male mice	Affects male reproduction by mitochondrial disruption	Reduction of microbiota diversity and composition changes	Hou *et al.* 2019
Mono-2-ethylhexyl ester (phthalate group)	Broad use in plasticizers	Pubertal male mice	Disruption of lipid metabolism, cholesterol imbalance, obesogene	Shift in microbiota composition, relative abundance of *Firmicutes* and reduction of *Verrucomicrobia*	Wang *et al.* 2019
Pentachlorophenol (PCP)	Pesticide used as herbicide, insecticide and molluscicide	Gold fish	Increase of oxidative stress, liver damage and reduction of body weight	Increase of phyla *Bacteroidetes, Bacteriodes,*decrease of *Firmicutes, Chrysobacterium, Microbacterium, Legionella, Anthrobacter*	Kan *et al.* 2015 F

*Some of these studies were also reviewed in the cited reviews. E – Evariste *et al.* 2019, F – Feng *et al.* 2018, R – Rosenfeld 2017, V – Velmurugan *et al.* 2017.

As demonstrated in mice, several EDs such as bisphenols compromise blood-testis barrier integrity and consequently sperm quantity and quality (Wu *et al.* 2019). Gut microbiota are necessary for proper formation of the blood-testis barrier (BTB), as demonstrated by increased BTB permeability in germ free mice. In these animals expression of proteins forming tight junctions of BTB (occludin, ZO-2 and E-cadherin) is reduced. Exposure of these animals to certain commensal bacteria as e.g. *Clostridium Tyrobutyricum*, which secretes short chain fatty acids, restored BTB integrity. Gut microbiota thus protects germ cells from environmental noxious substances including endocrine disruptors (Al-Asmakh *et al.* 2014).

As many as 450 compounds including the main classes of EDs possess estrogenic activity and as such affect reproductive functions in both females and males (Kiyama and Wada-Kiyama 2015). One of the key steroid metabolizing enzyme is β-glucuronidase. Gut microbial β-glucuronidase enzymes are a part of the the estrobolome, the collection of microbial reactions involving estrogens, which reactivate estrogens and regulate their circulating levels (Ervin *et al.* 2019). Recent experiments gave evidence that some estrogenic EDs may undergo glucuronisation (Andra *et al*. 2016). It can be expected that gut microbiota would participate in this reaction.

Polycystic ovary syndrome (PCOS), one of the most common female reproductive disorder, is characterized among other by steroid hormone dysregulation resulting in hyperandrogenemia. Recent studies have shown that it is often associated with gut microbiota dysbiosis, characterized by decreased bacteria diversity and changes in specific *Bacteroidetes* and *Firmicute* phyla (Thackray 2019). Using letrozole-induced PCOS mouse model, the causative role of gut microbiome dysbiosis in PCOS was proven (Torres *et al*. 2019). Association between PCOS and exposure to various endocrine disruptors has been repeatedly described and reviewed (Hu *et al.* 2018, Barrett and Sobolewski 2014, Palioura and Diamanti-Kandarakis 2015). It concerns first of all those compounds with (anti)estrogenic activity as bisphenol A (Hu *et al.* 2018). BPA concentrations in serum are higher in women with PCOS than in healthy women, but the causality, in contrast to animals, has not been established. Further work is needed to understand the mechanisms by which EDs contribute to PCOS and how changes in microbiota composition can contribute to counteract the effects of EDs.

Endocrine disruptors, gut microbiota, diabetes, obesity and related disorders

Many endocrine disruptors act as obesogens and are involved in exacerbation or even are responsible for diabetes of both types (for number of papers see Table 1). It concerns all main classes of EDs as bisphenols, phthalates, polychlorinated biphenyls, organochlorine pesticides, dioxins and parabens (Ruiz *et al.* 2018). As such, EDs increase adipogenesis by promoting the responsive genes, affect the mechanisms of hormone regulation of food intake, appetite and satiety, influence rest fuel metabolism, may cause disruption of pancreatic β-cell function an worsen insulin sensitivity; only typical reviews are cited here (Chevalier and Fénichel 2015, Casals-Casas and Desvergne 2011, Bodin *et al.* 2015, Petrakis *et al.* 2017).

Hundreds of recent reviews addressed also the issue of the role of gut microbiota in obesity, diabetes and related disorders including the metabolic syndrome, as e.g. Barlow *et al.* 2015, Maruvada *et al.* 2017, Bouter *et al.* 2017, Chen and Devaraj 2018, Vallianou *et al*. 2018. Generally, almost all the above disorders are associated with changes of gut microbiota in sense of reduction of commensal bacteria and dysbiosis. However, in the next paragraph(s) let us show a few concrete situations where EDs and gut microbiota act in parallel or are meeting:

Bisphenol A and many other EDs affect insulin synthesis and/or release by pancreatic β-cells and insulin signaling within insulin-sensitive organs including gut, which may lead to insulin resistance (Le Magueresse-Battistoni *et al.* 2018). Opening of the calcium channel and influx of Ca^{2+} ions into the cells is the last step of signaling cascade in the regulation of insulin release (by exocytosis) from β-cells after uptake of glucose. Bisphenol A can interact with Ca^{2+} channel resulting in insulin resistance (Ahn *et al*. 2018). A causal link between the intestinal microbiota dysbiosis and insulin resistance was confirmed in both rodents and humans (Saad *et al*. 2016). The latter authors summed up the mechanisms through which microbiota may act. It would be of interest to look for other common points linking the effect of EDs and microbiota.

One of the effects of microbiota is its influencing gastrointestinal mucosa permeability (compare the effect on blood-testis barrier). By fermentation of dietary polysaccharides they produce short-chain fatty acids, which, through their membrane

receptors in intestinal mucosa, may alter tight junctions between the cells (Blandino 2016). Exposure to some EDs, namely polychlorinated biphenyls also resulted in disruption of gut permeability *via* decreased expression of tight junctions proteins (Choi *et al.* 2010).

The fungicide tributyltin (an organometallic compound with tin) is a potent obesogen which induces adipogenesis by interacting with nuclear PPARγ and its heteromeric partner retinoid X receptor. Recent report showed that at least in mice tributyltin treatment decreased gut microbial species and changed the microbiome composition (Guo *et al.* 2018).

Endocrine disruptors, gut microbiota and immunity

There are many examples how EDs affect both innate as well as acquired immunity as evident from Table 1; for recent review see e.g. Bansal *et al.* 2018. EDs affect the development, differentiation and functions of various immune cells, lymphocytes, monocytes, dendritic cells, neutrophils, mast cells, eosinophils and natural killers (Nowak *et al.* 2019). The commensal gut microbiota regulates the maturation of the mucosal immune system, while the pathogenic microbiome causes immunity dysfunction, resulting in disease development. The gut mucosal immune system constitutes a protective barrier for the integrity of the intestinal tract. Endocrine disruptors and other toxicants may impair the function of mucosal intestine barrier (Coruzzi 2010, Feng *et al*. 2018), similarly as do pathogenic microbiota (Takiishi *et al.* 2017).

EDs may cause or exacerbate immunity-related diseases as diabetes, asthma, allergy and endocrine autoimmune diseases (Nowak *et al*. 2018). The parallel action of endocrine disruptors and gut microbiota on development of diabetes and insulin resistance was discussed in the previous chapter.

Endocrine disruptors are believed to contribute to development of autoimmune endocrinopathies, including the most frequent ones, autoimmune thyroid diseases (AITD), as evidenced indirectly by higher prevalence of AITD in polluted areas (Benvega *et al*. 2020). Among EDs the prominent one is BPA due to its immune stimulatory activity (Aljadeff *et al*. 2018). Gut microbiota *via* its surface signaling molecules and metabolic products can communicate with cells of innate immune system. Under dysbiosis this communication is disturbed and thus might contribute to development of autoimmunity (Thaiss *et al.* 2016). Generally, gut microbiota dysbiosis has been repeatedly observed in many autoimmune diseases as intestinal autoimmune diseases, type 1 diabetes mellitus, systemic sclerosis, systemic lupus erythematosus and last but not least in autoimmune thyroid disease (AITD), first of all in the most frequent autoimmune disorder worldwide, Hashimoto's thyroiditis (Virili *et al*. 2018).

Another widespread group of autoimmune disorders of Western population is inflammatory bowel disease. Hundreds of original papers, metaanalyses and reviews gave evidence for its relation to composition and structure of gut microbiota (Sartor and Wu 2017, Nishida *et al*. 2018), while only a few pointed so far to involvement of EDs, suggesting the way for further research (de Silva *et al.* 2017).

Endocrine disruptors, gut microbiota and mental disorders

As apparent from Table 1, endocrine disruptors can influence the brain development and actions. A crucial role for optimal brain function during prenatal period as well as during maturity and even senescence play gonadal hormones, in concert with thyroid hormones. They are indispensable in the processes of neurogenesis, they protect against neurodegenerative disorders and support cognitive activities. The impact of EDs consists in affecting hormonal mechanism of action by interacting with the respective receptors and signaling, and influencing hormone biosynthesis (Sanderson 2006). In addition EDs may act directly by modulation of neuronal transmission (Weiss 2011, Schug *et al*. 2015). As such, EDs are involved in onset and development of most severe neurodegenerative diseases (Alzheimer´s and other dementias, Parkinsonism, multiple sclerosis). As shown in previous paragraphs, EDs contribute to impairment of insulin signaling and sensitivity, one of characteristic features (signs) of Alzheimer´s dementia (Wang *et al.* 2017). More recent reports point also to their harmful neurobehavioral effects including autistic spectrum disorders (Tareen and Kamboj 2012).

Gut microbiota is capable to synthesize and metabolize steroid hormones and as such contribute to their circulating levels and indirectly affect the brain development and function (Vom Steeg and Klein 2017). Less information is available as concerns the role of microbiota in thyroid hormone biosynthesis and metabolism (Virili and Centanni 2017). Many reports

provide evidence for association of neurodegenerative- and even neuropsychiatric diseases with gut microbiota dysbiosis (Jiang *et al.* 2017, Colpitts and Kasper 2017, Dopkins *et al.* 2018, Stefano *et al.* 2018). As mentioned already, endocrine disruptors belong to environmental factors causing gut microbiota dysbiosis (Velmurugan *et al.* 2017, Rosenfeld 2017), indicating a link between both players. While the effects of EDs on biochemical and molecular levels are in most instances known, the causal relationship between the effects of microbiota is not clear so far; it would be interesting to look for mechanisms responsible for these effects.

Besides gonadal steroids let us mention the glucocorticoids and their role in neuroendocrine signaling in the axis microbiota-gut-brain. An important peripheral enzyme regulating actual concentration of glucocorticoids is 11β-hydroxysteroid dehydrogenase type 1, which is the target of various EDs and belongs also to enzymatic arsenal of gut microbiome (Ohshima *et al.* 2017, Johnson *et al.* 2017).

Conclusion

Environmental pollutants known as endocrine disruptors affect various physiological functions and are responsible for some harmful effects, manifesting themselves as various diseases or their exacerbation. Large body of literature is available about their effect on reproduction, immunity, development of diabetes and related disorders and even on mental health. Gut microbiome, a composition of bacteria and other microorganisms, co-existing in the gut with the host, is now believed to function as an autonomous endocrine organ, participating in endocrine and neuroendocrine regulations. The dysbiosis, a state consisting in an imbalance between commensal, beneficial bacteria and pathogens, often results in a disease.

Generally EDs can cause dysbiosis. While there is a lot of reports, reviews and metaanalyses dealing with the effects of EDs on one side, and analogically on the role of microbiome and its association with various physiological or pathological states on another, the literature on the mutual relationships between EDs and gut microbiome is relatively scarce.

The aim of this review is not only to show the ways and examples how EDs influence the function of gut microbiome, but first of all to point to connecting links where both players are meeting, i.e. act in parallel or against one another, even though the mechanisms staying behind may differ. We believe that it could suggest the way for further research.

Conflict of Interest

There is no conflict of interest.

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