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Review article

Neuropeptides in the microbiota-brain axis and feeding behavior in autism spectrum disorder

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ABSTRACT

A combination of altered social and feeding behaviors is common in children with autism spectrum disorder (ASD); however, the underlying mechanisms are unknown. Nevertheless, it has been established that several specific neuropeptides are critically involved in the regulation of both feeding and social behavior, such as α-melanocyte-stimulating hormone (α-MSH) and oxytocin, respectively. Moreover, recent data implicated gut microbiota in regulation of host feeding and emotion and revealed its dysbiosis in ASD, suggesting a mechanistic role of altered microbiota–brain axis in ASD. In this review, we discuss how gut microbiota dysbiosis may alter hunger and satiety peptide hormones as well as brain peptidergic pathways involved in the regulation of host feeding and social behaviors and hence may contribute to the ASD pathophysiology. In particular, we show that interactions between α-MSH and oxytocin systems in the brain can provide clues for better understanding of the mechanisms underlying altered feeding and social behaviors in ASD and that the origin of such alterations can be linked to gut microbiota.

Introduction

Altered feeding behavior is a common feature in children with autism spectrum disorder (ASD) adding to the main pathologic characteristics of impaired communication and social interaction [1]. Typical alterations include both food refusal and aversion based on food texture and appearance or presentation of new food [2,3]. Although individuals with ASD consume sufficient amount of calories and do not typically display symptoms of malnutrition such as weight loss, selective deficits of some vitamins and microelements can be present, mainly owing to inadequate consumption of fruits and vegetables [4,5]. Decreased appetite in ASD also has been revealed as part of depression-like symptoms [6]. Taken together, the restrictive feeding behavior in ASD points to specific abnormalities in the brain control of appetite. This control involves hunger and satiety peptide hormones from the gut acting on the brain anorexigenic and orexigenic neuropeptidergic circuitries constituting the gut–brain axis, which interacts with the dopaminergic reward system [7]. In light of increasing knowledge of molecular mechanisms responsible in appetite control in normal and pathologic conditions, it is possible to gain new insight into the origin of altered feeding behaviors in ASD by looking at the overlap between the peptidergic pathways that regulate feeding and social behaviors. Indeed, social behavior is intimately linked to feeding at basic behavioral levels as long as food acquisition and consumption involves interactions between individuals [8]. Furthermore, gut microbiota appeared recently as a major player in the regulation of various physiological processes including brain development and behavior relevant to ASD [9–11]. The involvement of gut peptides in the microbiome–brain axis relevant to anxiety and depression recently was reviewed [12]. In the present review, we discuss a possible mechanistic link between the gut microbiota–brain axis and altered feeding behaviors in ASD, mainly by analyzing the role of neuropeptides and peptide hormones in regulation of appetite and social behaviors.

Gastrointestinal symptoms and feeding behavior in ASD

According to the *Diagnostic and Statistical Manual of Mental Disorders*, ASD is characterized by impaired verbal or nonverbal

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communication and social interactions, and stereotyped or repetitive behavior [13]. ASD is a neurodevelopmental disorder that begins in early childhood and appears with the notable incidence of 1% to 2%, according to different studies conducted in Asia, Europe, and North America [14–16]. ASD incidence is sex-dependent: It is about 4.5 times more frequent in boys and is found in all races, ethnicities, and socioeconomic groups [17]. As a clinical and biological phenomenon, ASD comprises a wide range of complex and multifaceted neurologic disorders and is believed to be multifactorial [18]. Identification of gastrointestinal (GI) abnormalities related to these factors is a complex task. They may vary in autistic patients, impeding the development of universal diagnostic methods and treatment regimens. From 9% to 91% of patients with ASD may present different GI problems correlating with ASD severity [19]. Dyspepsia is dominated by constipation and diarrhea often accompanied by abdominal pain, vomiting, and gastroesophageal reflux [20].

Furthermore, ~90% of children with autism display aberrant feeding behaviors [21]. They are picky eaters whose diet is usually limited to a very narrow range of foods depending on their type, texture, or appearance. These children prefer starchy and fatty foods, simple carbohydrates, snacks, and processed foods over fruits, vegetables, and proteins (meat, fish, or eggs) [1]. Children with ASD display extreme nutrient sensitivity; their behavior is directly dependent on the eaten food. This connection may not be so obvious in healthy children, but children with autism are apparently more susceptible to the effects of microbial and bodily metabolites. Non-allergic intolerance of gluten/gliadin manifests itself as hyperactivity, agitation, aggression, auto-aggression, lethargy, sleepiness, and dyspepsia. Hydrolyzed into polypeptides (casomorphins) with an opioid-like effect on the nervous system, cow's milk induces similar behaviors. Sometimes excluding gluten- or casein-containing foods from a child's diet can help improve or control the aforementioned symptoms [22,23]. Despite breastfeeding difficulties and the lack of nutrients early in life, 10% to 58% of children with autism grow to become overweight or obese [24]. As a rule, food selectivity has long-term, negative effects on health including cardiovascular and bone density problems [25,26]. Therefore, causes of food selectivity should be identified to correct aberrant eating habits in children with autism.

Nutritional factors may contribute to the development of ASD via low provision of polyunsaturated fatty acids (PUFAs) [27]. Indeed, children with ASD display lower serum levels of ω-3 PUFA: docosahexaenoic acid) and of ω-6 PUFA, arachidonic acid, both the main constituents of nerve cells as well as of essential ω-6 PUFA linoleic acid [28]. This suggests insufficient intake of fish, meat, and nuts, respectively. Indeed, some studies revealed low intake of foods containing PUFAs [29]. Supplementation of children with autism with ω-3 PUFAs was, therefore, recommended [30]. Arabinitol is a sugar alcohol derived from arabinose in a process catalyzed by gut microorganisms such as fungus *Candida albicans*. Increased levels of arabinitol was found in ASD and it was reduced after a probiotic treatment [31].

Symptoms of dyspepsia and aberrant feeding behavior may be related to the altered digestive and metabolic functions of gut microbiota [32]. One of the major functions of a healthy microbiome is breakdown of complex plant-derived polysaccharides and other “non-digestible” bioactive substances. Refusal to eat certain foods to avoid postingestive pain can be the only sign of dyspepsia in patients who lack social skills to communicate their problems. The deficiency of microbial digestive capacity in children with ASD may lead to abdominal pain or discomfort as well as inflammatory processes, oxidative stress, altered gut barrier, bloating, or flatulence [33].

Feeding behavior and neuropeptides in the gut-brain axis and ASD

Gut bacteria are involved in appetite regulation via bacteria-derived molecules produced during different bacterial growth phases that interact with the host molecular pathways of hunger and satiety, acting locally in the gut at short-term but also influencing the brain at long-term appetite control [34]. Therefore, it is conceivable that specific microbiota-derived molecules interfering with the host hunger and satiety peripheral and central pathways also may participate in mechanisms of altered feeding behavior in ASD. Such possibility is in line with a theory of the role of opioid-like food-derived peptides in ASD [35,36]. This theory was formulated by Sahley and Panksepp who proposed that the increased levels of endogenous opioid peptides may alter social behavior and can produce autistic-like symptoms [37]. β-endorphin is one of the opioid peptides that affects social behavior [38]. It is of interest that β-endorphin is a product of cleavage of its prepropeptide precursor proopiomelanocortin (POMC), which gives rise to other bioactive peptides including α-melanocyte-stimulating hormone (α-MSH), one of the main anorexigenic neuropeptides in the brain acting on melanocortin (MC) receptors type 4 (MC4R) [39]. Furthermore, neurons producing brain-derived neurotrophic factor (BDNF) appear as MC4R-mediated downstream targets of α-MSH in producing anorexigenic effects [40]. In turn, altered BDNF signaling in the brain has been implicated in ASD pathophysiology [41]. In addition to the central nervous system, MC receptors also are present in the gut and may contribute to the signaling of intestinal satiety [42].

Whether abnormal stimulation of POMC neurons in the brain may exist in ASD is unknown, but it is conceivable that such stimulation may increase simultaneous or independent β-endorphin and α-MSH production, leading to altered social behavior and reduced feeding, respectively. Indeed, α-MSH independent release of β-endorphin by POMC neurons has been reported in response to endocannabinoids, which inhibit POMC neurons at low doses and excite at higher doses [43,44]. A bimodal effect of endocannabinoids relevant to feeding behavior also was observed in other brain areas, including the ventral striatum, the brain area regulating feeding reward [43,44]. It is interesting that in contrast to α-MSH, β-endorphin stimulates feeding behavior via μ-opioid receptors contributing to a non-homeostatic regulation of appetite [43]. In fact, β-endorphin and other opioid peptides are known as key signals in the reward system of motivated behavior including feeding [45]. Whether gut bacteria may produce opioid-like peptides or influence their production from nutrients is not yet known, but they regulate host production of endocannabinoids [46]. For instance, oral administration of specific *Lactobacillus* strains induced the expression of μ-opioid and cannabinoid receptors in intestinal epithelial cells [47]. A therapeutic utility of enhancing the endocannabinoid system in ASD recently was reviewed [48].

The principal source of POMC neurons in the brain is the hypothalamic arcuate nucleus, located in the vicinity of a circumventricular organ accessible to systemically circulating signaling molecules. Several peptide hormones from the gut and other organs and tissues are known to activate arcuate POMC neurons. Leptin, a hormone regulating long-term energy balance produced mainly in the adipose tissue but also in the stomach, can directly activate POMC neurons [49,50]. Plasma levels of leptin were reported to be elevated in autism [51,52] and can be further increased together with body mass index after chronic ASD treatment by risperidone [53]. Leptin is also able to activate POMC neurons indirectly by diminishing an inhibitory γ-aminobutyric acid (GABA) tone from neighboring neuropeptide Y (NPY) neurons of

the arcuate nucleus [54]. NPY neurons are involved in the orexigenic brain circuitry and are activated by ghrelin, a peptide hormone produced in the stomach and stimulated by negative energy balance [55]. It is remarkable that plasma ghrelin levels are decreased in children with ASD [51]. The possible role of gut microbiota in producing such changes can be suspected because increased plasma levels of leptin and decreased ghrelin are typically found in obesity which, in turn, is characterized by modification of bacterial composition for instance increased ratios of *Firmicutes* to *Bacteroidetes* [56]. Children with ASD also may display such ratios [57–59], however, this finding is not consistently reproduced in either obese or autistic individuals [60,61]. These data point to existence of obesity-independent mechanistic links between gut microbiota and energy balance–related hormones such as leptin and ghrelin.

POMC neurons also can be activated by caseinolytic protease B analogue (ClpB), a 96 KDa bacterial protein produced be *Enterobacteriaceae* [62]. Such ability of ClpB is probably owing to its molecular mimicry with α-MSH [63]. In fact, a ClpB fragment containing α-MSH-epitope was able to activate MC1 receptor [64]. Increased presence of *Enterobacteriaceae* was found in gut microbiota of patients with anorexia nervosa [65] and it was also reported for ASD [66]. The role of ClpB in activation of POMC neuron need, further studies including identification of the cellular receptor pathway and possible distinct effects on α-MSH and β-endorphin release.

Among the principal downstream target of the arcuate NPY neurons involved in stimulation of appetite is the paraventricular hypothalamic nucleus (PVN), where NPY can inhibit oxytocin-producing neurons [67]. Oxytocin is involved in a variety of physiological functions including a major role in promotion of social behavior [68]. Such role of oxytocin places it as a possible target in ASD. Indeed, plasma oxytocin levels are decreased in ASD [69] and patients with ASD receiving oxytocin intranasally show improvement in social communications [70]. In experimental settings, oxytocin treatment prevents social and learning deficits in mice deficient in the *Magel2* gene, involved in ASD [71]. Mutation of another gene, encoding contactin-associated protein-like 2 (*Cntnap2*) results in a lower number of oxytocin neurons in the hypothalamic PVN and altered social behavior, which can be improved by administration of oxytocin or MC4 receptor agonist, which stimulates endogenous oxytocin release [72]. Moreover, contactin-deficient mice are anorectic and show abnormal expression of neuropeptides in the arcuate nucleus [73]. These examples illustrate an intrinsic mechanistic link between the melanocortin and oxytocin signaling systems in the regulation of feeding and social behaviors. Moreover, in addition to the homeostatic control of feeding, oxytocin enhances rewarding properties of social interactions in the nucleus accumbens interacting with the serotonin system [74] and increases endocannabinoid mobilization in this brain area [75]. Regarding the possible influence of gut microbiota, it was shown that supplementation of mice with *Lactobacillus reuteri* in drinking water increased plasma levels of oxytocin [76]. The same group of researchers more recently showed that a lysate of *L. reuteri* also was able to increase plasma oxytocin as well as the number of oxytocin-immunopositive neurons in the caudal part of PVN in mice [77]. These results suggests that *Lactobacilli* are able to produce signaling molecules upregulating oxytocin release. This was further corroborated in a study showing a decrease of *L. reuteri* in gut microbiota composition of mice born from mothers fed high-fat diets and displaying social deficits and low numbers of oxytocin neurons in the PVN [78]. Importantly, reintroduction of *L. reuteri* to these mice restored both social deficit and oxytocin neurons [78]. However, the data on *Lactobacilli* content in gut microbiota of patients with ASD are inconsistent, showing either decrease or increase [58,59,79]. Thus, future studies should identify the bacterial molecules responsible for oxytocin release and determine whether their production is specific for certain *Lactobacillus* species.

The intestinal satiety hormones activate brain anorexigenic pathways directly via the circulation and circumventricular organs or via the vagus nerve. Cholecystokinin (CCK) is a classical satiety hormone produced in the duodenum with a peak of secretion about 15 min after a meal [80]. It is of interest that CCK administration stimulates oxytocin secretion into the systemic circulation by selective activation of hypothalamic PVN and supraoptic oxytocin neurons [81]. The data on CCK levels in ASD are very limited. One study reported no differences of CCK levels in blood mononuclear cells, whereas the patients with ASD from the same study showed increased levels of β-endorphin [82]. Absence of gut flora in mice results in lower production of CCK and increased levels of secretin, but more detailed data linking these hormones with gut microbiota are missing [83]. Secretin is another satietogenic peptide hormone produced in the small intestine that reduces food intake via activation of the MC system [84]. Secretin also activates oxytocin neurons in the PVN, although in a less extent than CCK [85]. Of interest, secretin but not CCK administration was tested in patients with ASD, although without significant improvement [84,86]. Thus, the relevance of a link between CCK and oxytocin to ASD pathophysiology and treatment opportunities needs further studies, including a possible involvement of gut microbiota.

Glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) are satiety hormones produced by the enteroendocrine L cells located primarily in the large intestine. Although produced by the same cells, these hormones have distinct meal-triggered dynamics of secretion with GLP-1 showing a peak at 15 min, similar to CCK, whereas increased levels of PYY are observed after 20 min and are maintained for 2 to 3 h [80]. To cause satiety, both hormones act locally in the gut to activate their receptors in the vagal afferents as well as in the brain where GLP-1 activates arcuate POMC neurons and PYY inhibits NPY neurons. The latter is possible due to PYY binding to Y2 receptor after PYY degradation in plasma to PYY 3-36 by the dipeptidyl peptidase [87]. Although there are no data implicating directly PYY and GLP-1 in autism, the GLP-1 role of an incretin (i.e., a hormone increasing insulin secretion) suggests its possible relevance to diabetes, which more frequently occurs in patients with autism [88,89]. Moreover, considering that PYY and NPY may inhibit the same neurons via binding to Y2R, and that NPY is co-released with GABA from arcuate NPY neurons, peripheral PYY may contribute to the insufficient GABA inhibition of brain targets relevant to impaired cognitive functions in ASD [90]. The inductive effects of gut microbiota in GLP-1 and PYY secretion is certain. In particular, it has been shown that short-chain fatty acids such as butyrate, produced during fermentation of non-digestible fibers, activate GLP-1 and PYY secretion [91]. Thus, nutritional deficit in foods rich in fiber in patients with ASD may contribute to insufficient production of GLP-1 and PYY and alter their normal role as intestinal satiety hormones. Specific *Lactobacillus* and *Bifidobacterium* species with high GABA production also may contribute to the microbiota–brain axis signaling, which can be altered in ASD [92].

Conclusion

Taken together, abnormal feeding behavior in ASD may involve uncoordinated secretion of GI hormones that are not able to activate in a timely manner brain anorexigenic and reward pathways to couple them with oxytocin secretion and, therefore,

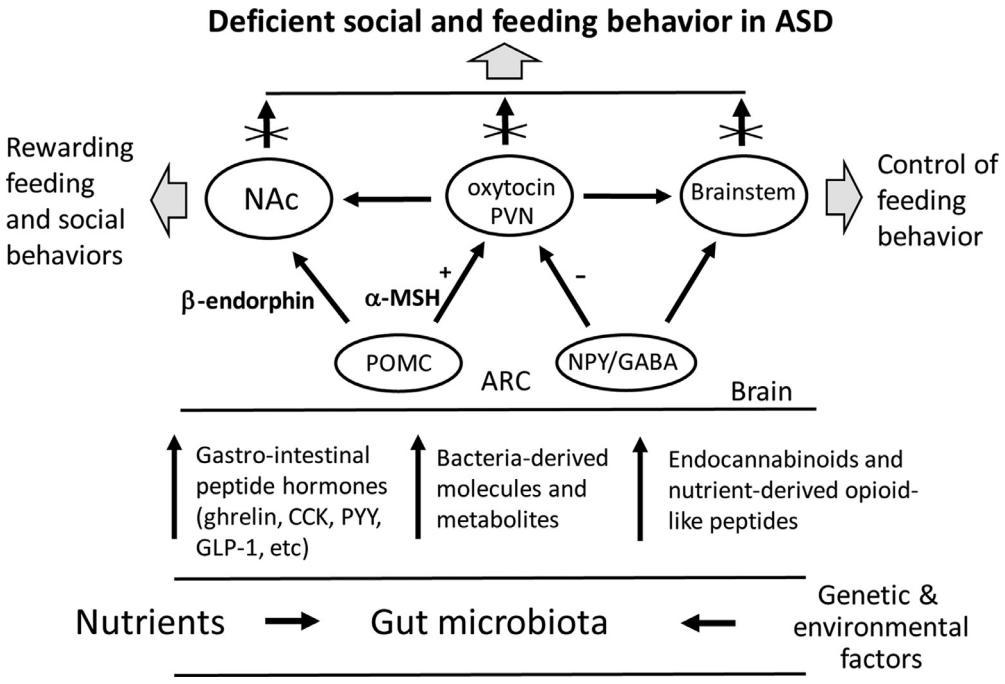

Fig. 1. Schematic positioning of neuropeptides and peptide hormones in the microbiota–brain axis involved in the regulation of feeding and social behaviors. It is notable that the several peripheral signals and neuronal circuitries are interconnected for the coordinated control of both feeding and social behaviors. Nutritional, genetic, and environmental effects on gut microbiota composition can be causative factors of dysbiosis present in ASD leading to the altered signaling in the microbiota–brain axis and deficient social and feeding behaviors. The exact nature of such signals involved in the ASD remains to be established. ARC, arcuate nucleus of the hypothalamus; ASD, autism spectrum disorder; CCK, cholecystokinin; GABA, γ-aminobutyric acid; GLP, glucagon-like peptide; NAc, *N*-acetylcysteine; NPY, neuropeptide Y; POMC, proopiomelanocortin; PVN, paraventricular hypothalamic nucleus; PYY, peptide YY.

reinforce the social aspects of eating (Fig. 1). Because gut microbiota participates in coordination of nutrient-induced activation of intestinal satiety, its implication in ASD is highly suspected. Future identification of gut bacteria-derived molecules that will be able to interfere with the brain oxytocin system directly or indirectly via the GI hormones may provide a new scientific background for ASD therapy.

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