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▶ **To cite this version:**

Sergueï O. Fetissov, Olga Averina, Valery Danilenko. Neuropeptides in the microbiota-brain axis and feeding behavior in autism spectrum disorder. Nutrition, Elsevier, 2019, 61, pp.43-48. 10.1016/j.nut.2018.10.030 . hal-02334083

**HAL Id: hal-02334083**

**https://hal-normandie-univ.archives-ouvertes.fr/hal-02334083**

Submitted on 21 Oct 2021

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Version of Record: https://www.sciencedirect.com/science/article/pii/S0899900718305525
Manuscript_7f2d7a316343e4a63ce109e8bc695f20

*Review article for Nutrition*

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

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**Running title:** Neuropeptides & microbiota-brain axis in ASD

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## Abstract

Combination of altered both social and feeding behaviors is common in children with autism spectrum disorder (ASD) but 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 behavior, 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 the clues for better understanding of the mechanisms underlying altered feeding and social behavior in ASD and that the origin of such alterations can be linked to gut microbiota.

*Key words*: Autism, brain, feeding, social behavior, neuropeptides, gut microbiota

## Introduction

Altered feeding behavior is a common feature in children with autism spectrum disorder (ASD) adding to the main pathological characteristics of impaired communication and social interaction (1). Typical alterations include both food refusal and aversion based on food texture, appearance or presentation of new food (2, 3). Although ASD subjects consume sufficient amount of calories and do not typically display symptoms of malnutrition such as body weight loss, selective deficit of some vitamins and microelement can be present, mainly due to low consumption of fruits and vegetables (4, 5). Decreased appetite in ASD has also been revealed as a 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 pathological conditions, it is possible to gain new insight into the origin of altered feeding behavior in ASD by looking at overlap between the peptidergic pathways regulating feeding and social behaviors. Indeed, social behavior is intimately linked to feeding at a basic behavioral levels as long as food acquisition and consumption involves interactions between subjects (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 has recently been reviewed (12). In this review we discuss a possible mechanistic link between the gut microbiota-brain axis and altered feeding behavior in ASD mainly by analyzing the role of neuropeptides and peptide hormones in regulation of appetite and social behavior.

## 1. Gastro-intestinal symptoms and feeding behavior in ASD

According to the Diagnostic and Statistical Manual of Mental Disorders, ASD is characterized by impaired verbal or nonverbal 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% - 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 males and is found in all races, ethnicities or socio-economic groups (17). As a

clinical and biological phenomenon, ASD comprises a wide range of complex and multifaceted neurological disorders and is believed to be multifactorial (18). Identification of gastro-intestinal 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 gastrointestinal problems correlating with ASD severity (19). Dyspepsia is dominated by constipation and diarrhea often accompanied by abdominal pain, vomiting and gastroesophageal reflux (20).

Furthermore, about 90% of autistic children display aberrant feeding behavior (21). They are picky eaters whose diet is usually limited to a very narrow range of foods depending on their type, texture or appearance and prefer starchy and fatty foods, simple carbs, snacks, and processed foods over fruits, vegetables and proteins (meat, fish or eggs) (1). Children with ASD display also extreme nutrient sensitivity; their behavior is directly dependent on the eaten food. This connection may not be so obvious in healthy children, but autistic children are apparently more susceptible to the impact 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). In spite of breastfeeding difficulties and the lack of nutrients early in life, 10% - 58% of autistic children 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 in order to correct aberrant eating habits in autistic children.

Nutritional factors may contribute to the development of ASD via low provision of polyunsaturated fatty acids (PUFA) (27). Indeed, children with ASD display lower serum levels of omega-3 PUFA: docosahexaenoic acid (DHA) and of omega-6 PUFA, arachidonic acid, both the main constituents of nerve cells as well as of essential omega-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 autistic children with omega-3 PUFA 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).

## 2. 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 which 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). It is, hence, conceivable that specific microbiota-derived molecules interfering with the host hunger and satiety peripheral and central pathways may also 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). Beta (β)-endorphin is one of the opioid peptides affecting 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 alpha (α)-melanocyte-stimulating hormone (α-MSH), one of the main anorexigenic neuropeptides in the brain acting on melanocortin receptors (MC) type 4 (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). Beside the central nervous system, melanocortin receptors are also 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 and excite at higher doses (43, 44). A bimodal effect of endocannabinoids relevant to feeding behavior was also 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 mu-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 know but they regulate host production of endocannabinoids (46). For instance, oral administration of specific Lactobacillus strains induced the expression of mu-opioid and cannabinoid receptors in intestinal epithelial cells (47). A therapeutic utility of enhancing endocannabinoid system in ASD has been recently 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 (BMI) after chronic ASD treatment by Risperidone (53). Leptin is also able to activate POMC neurons indirectly by diminishing an inhibitory gamma (g)-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, peptide hormone produced in the stomach and stimulated by negative energy balance, (55). It is remarkable that plasma ghrelin levels are decreased in ASD children (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). ASD children may also display such ratios (57-59), however, this finding is not consistently reproduced neither in obese nor autistic subjects (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 can also be activated by caseinolytic protease B analogue (ClpB) a 96 KDa bacterial protein produced be *Enterobacteriaceae* (62). Such ability of ClpB is probably due 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 neurons needs, however, 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 ASD patients receiving oxytocin intranasally show improvement of social communications (70). In experimental settings, oxytocin treatment prevents social and learning deficit in mice deficient for the *Magel2* gene, involved in ASD (71). Mutation of another gene, encoding contactin-associated protein-like 2 (*Cntnap2*) results in 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 intrinsic mechanistic link between the melanocortin- and oxytocin- signaling systems in the regulation of feeding and social behavior. Moreover, beside the homeostatic control of feeding, oxytocin enhances rewarding properties of social interactions in the nucleus accumbens interacting with the serotonin system (74) and increases endocannabinoids mobilization in this brain areas (75). With regard to 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 Erdman more recently showed that a lysate of *Lactobacillus reuteri* was also 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 *Lactobacillus reuteri* in gut microbiota composition of mice born from mothers fed high fat diet and displaying social deficit and low number of oxytocin neurons in the PVN (78). Importantly, reintroduction of *Lactobacillus reuteri* to these mice restored both social deficit and oxytocin neurons (78). However, the data on lactobacilli content in gut microbiota of ASD patients are inconsistent showing either decrease or increase (58, 59, 79). Thus, future studies should identify the bacterial molecules responsible of 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 has reported no differences of CCK levels in blood mononuclear cells, while the ASD patients 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 which reduces food intake via activation of the melanocortin 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 ASD patients, 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, while increased levels of PYY are observed after 20 min and are maintained for 2-3 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 autistic patients (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 fibers in ASD patients 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 may also contribute to the microbiota-brain axis signaling which can be altered in ASD (92).

## 3. Conclusion

Taken together, abnormal feeding behavior in ASD may involve uncoordinated secretion of gastro-intestinal hormones which are not able to timely activate brain anorexigenic and reward pathways to couple them with oxytocin secretion and, therefore, reinforce the social aspect of eating (Figure 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 which will be able to interfere with the brain oxytocin system directly or indirectly via the gastro-intestinal hormones may provide a new scientific background for ASD therapy.

**Acknowledgements**

SOF is supported by the Transversal Microbiota Program, Inserm, France.

OVA is supported by the grant 17-15-01488 from Russian Science Foundation, Russia.

**Conflicts of interest**

SOF is a co-founder of TargEDys, SA and its consultant. Other co-authors did not declare conflict of interest.

**Figure legend**

**Figure 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 impact 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.

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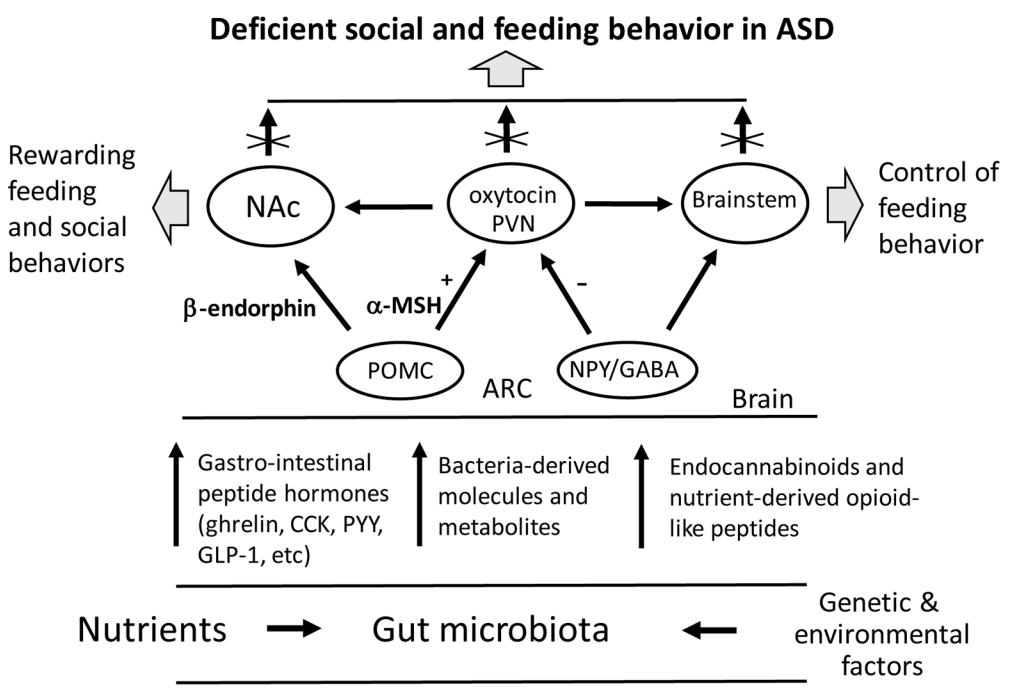
Deficient social and feeding behavior in ASD
Rewarding feeding and social behaviors
NAc
oxytocin PVN
Brainstem
Control of feeding behavior
β-endorphin
α-MSH
+
-
POMC
ARC
NPY/GABA
Brain
Gastro-intestinal peptide hormones (ghrelin, CCK, PYY, GLP-1, etc)
Bacteria-derived molecules and metabolites
Endocannabinoids and nutrient-derived opioid-like peptides
Nutrients
Gut microbiota
Genetic & environmental factors

Figure 1