

REVIEW ARTICLE

Microbes, oxytocin and stress: Converging players regulating eating behavior

Cristina Cuesta-Marti^{1,2} | Friederike Uhlig^{2,3}  | Begoña Muguerza^{1,2,4}  |
Niall Hyland^{2,3} | Gerard Clarke^{2,5} | Harriët Schellekens^{1,2} 

¹Department of Anatomy & Neuroscience, University College Cork, Cork, Ireland

²APC Microbiome Ireland, Cork, Ireland

³Department of Physiology, University College Cork, Ireland

⁴Universitat Rovira i Virgili, Department of Biochemistry & Biotechnology, Nutrigenomics Research Group, Tarragona, Spain

⁵Department of Psychiatry & Neurobehavioural Science, University College Cork, Cork, Ireland

Correspondence

Harriët Schellekens, Department of Anatomy and Neuroscience, University College Cork and APC Microbiome Ireland, Cork, Ireland. Email: h.schellekens@ucc.ie, 120108071@umail.ucc.ie

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Abstract

Oxytocin is a peptide-hormone extensively studied for its multifaceted biological functions and has recently gained attention for its role in eating behavior, through its action as an anorexigenic neuropeptide. Moreover, the gut microbiota is involved in oxytocinergic signaling through the brain-gut axis, specifically in the regulation of social behavior. The gut microbiota is also implicated in appetite regulation and is postulated to play a role in central regulation of hedonic eating. In this review, we provide an overview on oxytocin and its individual links with the microbiome, the homeostatic and non-homeostatic regulation of eating behavior as well as social behavior and stress.

KEYWORDS

brain-gut axis, eating behavior, food intake, food reward, G-protein coupled receptors (GPCRs), gut microbiota, microbiota-gut-brain axis, oxytocin, social behavior, stress

1 | INTRODUCTION

Oxytocin (Oxt) is a neuropeptide that is synthesized in the hypothalamus and secreted into the brain as well as the bloodstream via the neurohypophysis.^{1–3} This peptide hormone has been implicated in a broad range of biological functions that are mediated through either central (sociability, bonding, stress response) or peripheral (contraction of the uterus, intestinal contractility and secretion, visceral pain) Oxt receptors (OXTRs).^{4,5} Over the last decade, increasing preclinical and clinical data has demonstrated the importance of Oxt in the regulation of food intake and energy balance, implicating this hormone as an anorexigenic signaling molecule because of its effects on

reducing appetite and bodyweight.^{4–6} More recently, increasing evidence suggests that Oxt also is a player in the central processing of reward.^{4,7} Oxt administration has been shown to modulate the preference of food types, and food pleasure in preclinical and clinical studies.^{4,8,9}

Oxt has also been investigated for its potential interaction with the human microbiota.¹⁰ This hormone seems to both impact and be modulated by the microbiome.^{11–13} For instance, Oxt administration (10 IU SC/animal/day, 14 days), induced changes in the gut microbiota composition in rats and was associated with overall improvement in stress, and anxiety/depression-like behaviors.¹¹ Noteworthy, the probiotic *Limosilactobacillus reuteri* (formerly known as

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Lactobacillus reuteri) has been shown to not only increase circulating Oxt levels¹² but also Oxt expression in the brain¹³ in rodents, effects which have been linked with metabolism,^{14,15} wound healing,¹² sociability and behavior.^{14,16,17} Whilst the effects of *Limosilactobacillus reuteri* have been reviewed elsewhere,¹⁶ recently other bacterial strains such as *Blautia stercoris* MRx006 and bacteria-derived metabolites, such as 4-ethylphenylsulfate (4EPS), have also demonstrated ability to modify social and sensorimotor behavior and hypothalamic Oxt expression in rodents.^{18,19} Furthermore, a recent randomized controlled trial performed by Narmaki et al.²⁰ showed that probiotic administration (multistrain probiotic $\approx 10^{10}$ CFU per day, 12 weeks) increased Oxt serum levels in obese women with food addiction.²⁰ The supplementation also resulted in a significant improvement in eating behavior, increasing cognitive resistance towards food intake.

Thus, the gut microbiota and Oxt signaling have independently been linked with food intake and eating behavior, which begs the question whether the microbiota can modulate homeostatic and/or hedonic aspects of food intake (e.g., food reward and food motivated behavior) via the Oxt system.

In this review, we give an overview of the Oxt neuropeptide and its physiological functions, with a particular focus on social behavior, stress and eating behavior. We highlight novel findings relating Oxt, the microbiome and eating behavior suggesting that microbiome-targeting interventions might modulate Oxt signaling and functionality, thereby affecting both homeostatic and non-homeostatic food intake. We also discuss the influence of the gut microbiome and Oxt signaling on eating behavior through their converging effect on social behavior and stress.

2 | OXYTOCIN AND OXYTOCIN RECEPTOR

2.1 | Oxytocin expression

The neuropeptide Oxt is encoded by the gene *Oxt* oxytocin/neurophysin I prepropeptide (Gene ID: 5020) which is located in the same chromosomal locus as the vasopressin (*Avp*) gene (*dAVP-neurophysin II* (*NPII*)) across all the species, both being adjacent paralogous genes in the chromosome 20p13 distanced by 12 kb of intergenic region and transcribed from opposite strands.²¹ The *Oxt* gene comprises two introns and three exons, of which exon 1 contains the sequence for the final OXT nonapeptide (further described in Figure 1).^{21,26} The rest of the gene encodes for a signal peptide and neurophysin I (also Oxt prepropeptide; 10-kDa and 125 amino acids length peptide) which serves as a carrier protein and is secreted along with Oxt. In the brain, Oxt synthesis occurs predominantly in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus as well as the medial preoptic area, and substructures of dorsomedial hypothalamic nucleus.^{2,3,27} As part of the hypothalamo-neurohypophysial system, Oxt vesicles produced in magnocellular oxytocinergic neurons are released into neurohypophysial capillaries from where it enters the bloodstream.

Oxytocinergic neurons have been found in the forebrain and other brain regions^{2,3,28} but it is not clear yet whether Oxt is released in these areas and if so, what the release mechanisms are (via dendrites, synapses or in a non-synaptic mode^{3,28,29}).

In addition to its expression in the brain, there is evidence for expression of Oxt in peripheral organs, in particular the uterus, corpus luteum, placenta, amnion, testes (interstitial cells), heart, adrenal glands, dermis (fibroblasts and keratinocytes), thymus, and the gastrointestinal tract.³⁰ The presence of these peripheral Oxt-producing cells, along with OxtR (see Section 2.2), suggests that there are local circuits that induce local Oxt secretion independent of the hypothalamus. In contrast to central Oxt release which is induced by physiological stimuli such as suckling, parturition, or stress,^{1,2} it is currently unknown how Oxt secretion from peripheral oxytocinergic cells is triggered.

2.2 | Oxytocin receptor

Central and peripheral effects of Oxt are mediated by the OXTR. The OXTR is encoded by the *Oxt* receptor gene (*Oxtr*) (Gene ID: 5021), which is expressed both peripherally² and centrally.

The OXTR belongs to the Class I G-protein-coupled receptor (GPCRs) and as such is comprised of seven hydrophobic transmembrane helices. Agonists, such as Oxt, bind a cavity of the OXTR between the α -helical segments of the transmembrane domains 3 and 6 also with involvement of residues within extracellular domains.²² Different binding sites have been shown between endogenous and synthetic Oxt agonists and antagonists.²² Studies using chimeric OXTR receptors suggested that Oxt antagonists may bind to transmembrane helices 1, 2, and 7, regions that are not involved in the Oxt binding.³¹ Moreover, it has been shown that Oxt binds and activates different OXTR GPCR subtypes depending on the neuropeptide concentration, for instance $G_{\alpha q/11}$ -signalling is activated at low Oxt concentrations whereas $G_{\alpha B}$ requires higher concentrations (Figure 2, top section).³² Depending on the receptor subtype, activation of the OXTR leads to the initiation of one of three different signaling pathways:^{2,28,32-34} the $G_{\alpha q/11}$ /PLC/InsP3 pathway, the $G_{\beta \gamma}$ /Raf/MEK/ERK1/2 and the $G_{\alpha i}$ - $G_{\alpha s}$ /AC/PKA (Figure 2). Although the precise OXTR signaling pathways in subpopulations of hypothalamic neurons, especially those regulating eating behavior, are still unknown, it is suggested that OXTR activation in the PVN involves the ERK and MAP kinase pathways (Figure 2).³⁵ Inhibition of this pathway prior to injection of Oxt abolished its anxiolytic effect in male rats.³⁵

In addition to OXTRs, Oxt also binds to the other GPCRs, including the *Avp* receptors V1aR, V1bR, and V2R, though with lower affinity than to OXTR.³⁶

Central *Oxtr* expression levels vary according to the organism,³⁷ the developmental stage³⁸ and sex.³⁹ The hypothalamus is a brain region with high *Oxtr* expression in both humans and mice (2-month-old) whereas high levels of hippocampal and cortical *Oxtr* expression have only been demonstrated in mice.³⁷ In mice, hippocampal OXTR protein expression is higher in embryonic and juvenile stages whereas

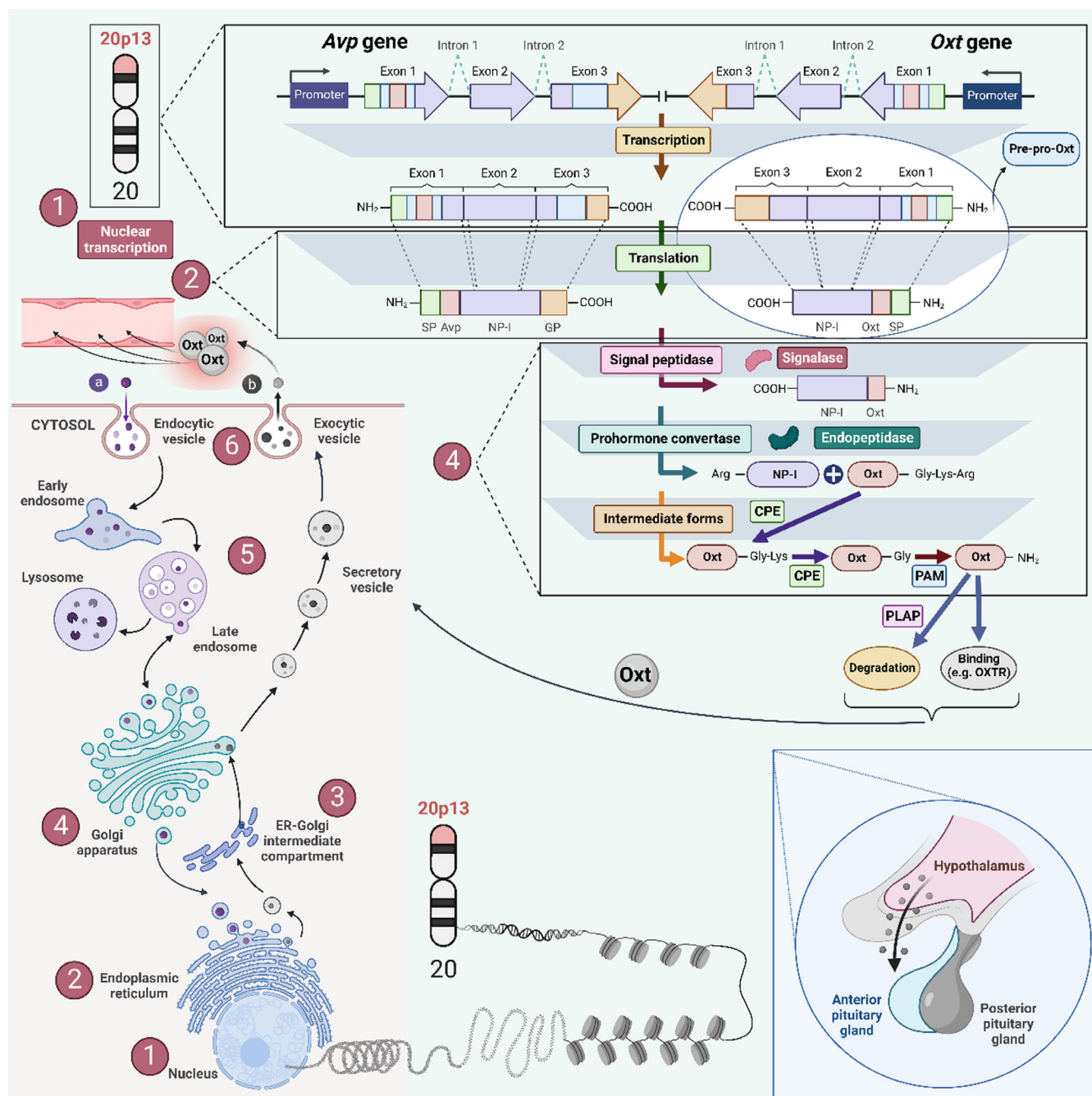


FIGURE 1 Representative scheme of the oxytocin (*Oxt*) and vasopressin (*Avp*) genes on the human chromosome 20 (chromosomal location 20p13) in addition to the *Oxt* biosynthesis and further modifications. *Oxt* and *Avp* genes are transcribed from opposite strands, and both are based on two introns and three exons. In the case of *Avp*, the first exon encodes different peptides (the AVP peptide, a signal peptide (SP), and the first residues of neurophysin (NP) peptide), the second encodes the central part of the NP peptide and finally, the third encodes a glycopeptide (GP) and the C-terminal region of NP. In the case of *Oxt*, the first exon encodes different peptides (the *Oxt* hormone, SP, and the first 9 residues of NP), the second exon encodes the central part of the NP and finally, the third one encodes the C-terminal region of NP. After the nuclear transcription of the genes, both *Avp* and *Oxt* prepropeptides are translated in the ribosomes of the rough endoplasmic reticulum (RER). The generated protein, we focus on *Oxt*, is transferred into the Golgi apparatus where concentration, packaging into neurosecretory vesicles and post-translational processing take place, which includes the action of a signal peptidase to release SP, and prohormone convertases that breaks down the peptide into NP-I and *Oxt*-Gly-Lys-Arg which generates *Oxt* after the action of a Carboxypeptidase E (CPE), α-amidating monooxygenase (PAM) and placental leucine aminopeptidase (PLAP) that cleave Arginine (Arg), Lysine (Lys) and Glycine, respectively. After the intravesicular post-translational process, *Oxt* is generated and the vesicles containing the neuropeptide are secreted from neuronal terminals into neurohypophyseal capillaries and into either the peripheral bloodstream or projecting to other brain regions. In the brain, *Oxt* synthesis occurs in the magnocellular hypothalamo-neurohypophyseal system, which involves mainly the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus (PVN). Informed by existing findings and figures from literature.^{2,22–25}

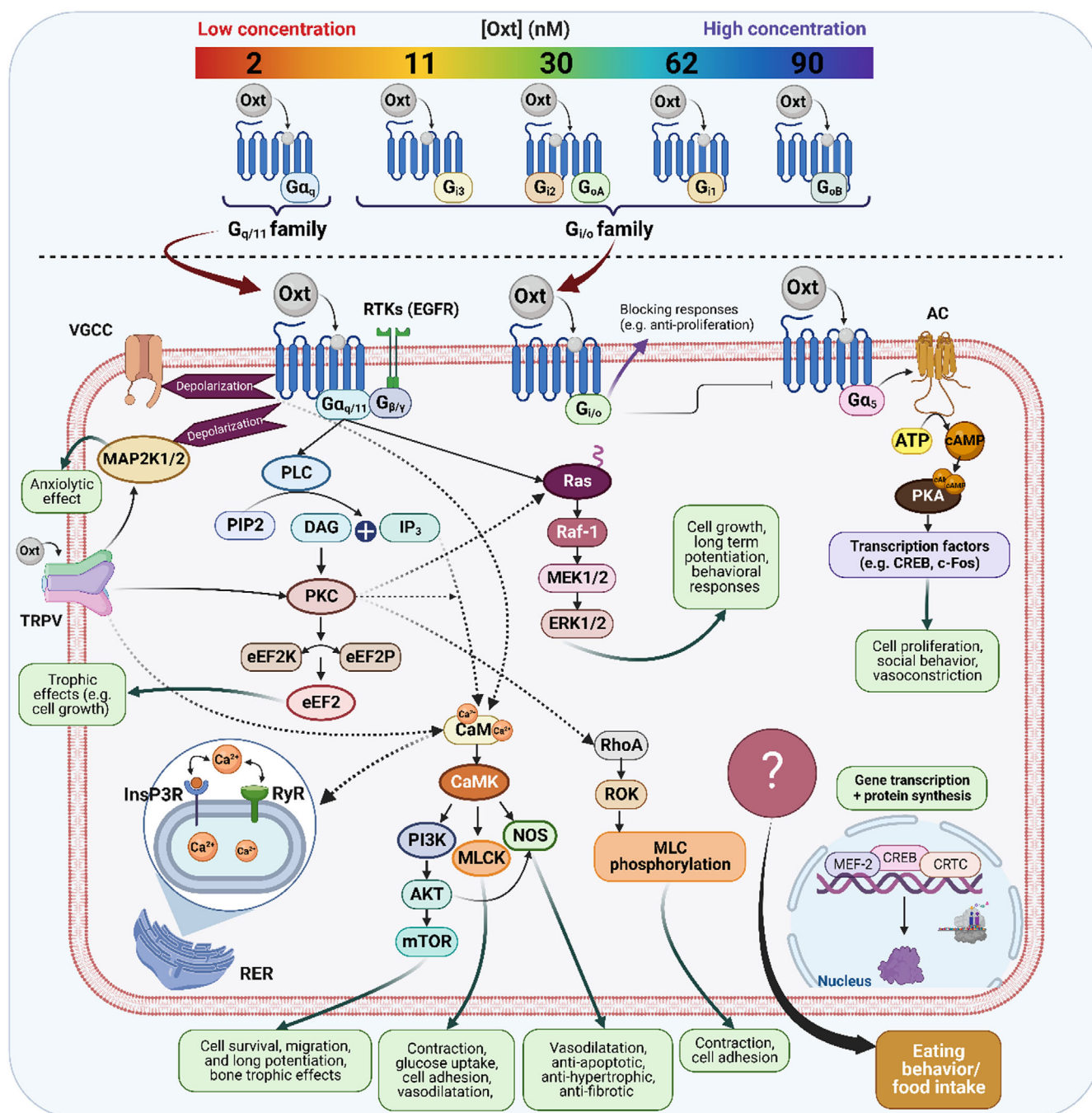


FIGURE 2 Legend on next page.

cortical OXTR expression increases during adulthood possibly relating to the relative importance of social and spatial memory and social decision making, respectively.³⁸ In addition, sex differences regarding OXTR in the hypothalamus and the posterior bed nucleus of the stria terminalis (integration of limbic and autonomic system) among others have been reported in both mice and rats.^{38,39}

Whilst there are two predominant OXTR mRNAs present in the brain (6.7 and 4.8 kb),⁴⁰ truncated versions have been found in peripheral tissues such as the uterus (2.9 kb) and ovaries (1.2 kb).⁴¹ Whether and how these genetic polymorphisms and epigenetic

mechanisms affect the downstream signaling is incompletely understood.^{42,43} However, in uterine myocytes, Oxt activates G_{α_{q/11}} and CAMK/MLCK downstream signaling to promote uterine contraction⁴⁴ whereas OXTR activation in endothelial cells induces G_{α_{q/11}}/phosphoinositide 3-kinase (PI3K)/Protein kinase B (AKT)/endothelial nitric oxide synthase (eNOS) signaling to enhance cardiomyogenesis (Figure 2).^{44,45} Peripheral expression of OXTR is highest in female reproductive organs,³⁷ and it is also expressed in the enteric nervous system of the gastrointestinal (GI) tract. Specifically, OXTR is expressed in neurons of the intrinsic nervous system of the GI tract,

and in sensory dorsal root ganglia and nodose ganglia neurons, where it has important gut-brain axis functions for gastrointestinal motility, inflammation, and visceral sensitivity.^{46,47} Whilst the existence of oxytocinergic neurons in the gastrointestinal tract has been appreciated for a while, further investigation is now warranted, particularly in the context of OXTR modulation by the microbiome.

2.3 | Modulation of oxytocin by the microbiome

The gut microbiota includes trillions of microbes including bacteria, archaea, viruses, and fungi that inhabit the gastrointestinal (GI) tract.⁴⁸ Through their interactions with diet, they produce numerous soluble mediators and cell wall components that have been shown to modulate gastrointestinal physiology, immune and metabolic function, brain-gut communication, and behavior.^{49–52}

Microbiota status and probiotics have been shown to affect Oxt levels, Oxt and Oxt_r expression (Table 1). For example, mice treated with antibiotics for >1 month displayed decreased Oxt_r expression levels in the frontal cortex and a trend for increased Oxt expression in the hypothalamus. In contrast, there were no significant differences between conventional (CONV) and germ-free (GF, animals raised without a microbiota) animals.⁵⁴ Another study, however, reported an increase of OXTR protein levels in specific cortical regions from male, but not female, GF rats.⁵⁵ To date, to the best of our knowledge, it is not known how microbial depletion affects blood Oxt levels. However, treating mice with the probiotic *L. reuteri* MM4-1A or humans with a multispecies-probiotic (3 *Bifidobacteria* and 3 *Lactobacilli*) increased plasma Oxt levels.²⁰

As with many microbiome-targeting interventions, the mechanism by which the microbiota affects Oxt expression in the brain is currently unclear. It is likely that it involves either bacterial metabolites in the circulation or vagal sensing of bacteria/bacterial products in the periphery leading to activation of oxytocinergic neurons in the brain, particularly the hypothalamus.¹⁷ These bacterial metabolites could also modulate the systemic immune system either directly or via gut-brain mediated pathways (i.e., neuroendocrine, vagal, immune) that affect central immunity and subsequent Oxt signaling.¹⁶ Alternatively, bacteria can modulate the secretion of neurotransmitters and peptides from hormone-releasing cells in the intestinal epithelium (serotonin, cholecystokinin, glucagon-like peptide, ghrelin) and the enteric nervous system that regulate gut-brain signaling⁶⁰ as well as intestinal physiology.^{52,61} This, in turn, affects the availability and absorption of nutrients, microbiota composition and thus, gut-brain communication.⁶² In addition to affecting central oxytocinergic neurons, the microbiota may also modulate enteric neurons that express Oxt or intestinal Oxt_r.⁶³ These neurons are strategically located in the submucous and myenteric plexus of the enteric nervous system and administration of Oxt indeed modulates intestinal ion transport and motility.^{63,64} Additionally, Oxt_r knock-out mice develop more severe colitis compared to control animals and Oxt can reduce intestinal inflammation.^{63,65} Because gut-innervating sensory neurons also express Oxt_r,⁴⁷ Oxt derived from enteric neurons is likely to play a role in regulating central Oxt release. The modulation of peripheral (gastrointestinal) Oxt and OXTR by the microbiota may directly contribute changes in central Oxt signaling or alternative changes in the brain via modulated gut-brain axis signaling, which warrants further investigation.

FIGURE 2 Scheme with G-protein coupled receptors (GPCRs) subtypes to which Oxt binds according to its concentration and signaling pathways of oxytocin (Oxt) and the respective effector actions (green box) via gene protein expression. Oxt binding to OXTR Gαq/11 subtype activates phospholipase C (PLC), which cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositoltrisphosphate (InsP3). Ca²⁺ is then released from the Ca²⁺ stores in rough endoplasmic reticulum (RER) via the binding of InsP3 to its receptor (InsP3R) or ryanodine receptor (RyR) in certain cells. DAG activates protein kinase C (PKC), which can activate in turn either Rho-mediated Rho kinase. PKC can also activate eukaryotic elongation factor (eEF2), which triggers multiple cellular responses such as protein synthesis in myometrial cells. Gαq/11 activation can cause membrane depolarization as well via activation for instance of voltage-gated Ca²⁺ channels (VGCCs), which mediate the Ca²⁺ signaling. When the intracellular Ca²⁺ ([Ca²⁺]_i) is increased, Ca²⁺ binds to the protein Calmodulin, which then induces the stimulation of calmodulin kinase (CaMK), activating finally diverse enzymes such as nitric oxide synthase (NOS) or phosphoinositide 3-kinase (PI3K) linked with cellular responses with peripheral Oxt actions, including cardiovascular, bone or muscle trophic effects. Additionally, Gαq-mediated OXTR activation can induce the transactivation of the epidermal growth factor receptor (EGFR; a receptor tyrosine kinase or RTK) which activates then the mitogen-activated protein kinase (MAPK) pathway mediated by MEK1/2. The complex Ca²⁺-CaM can also activate myosin light-chain kinase (MLCK), which induces myometrial contraction. Finally, Gαq-mediated OXTR activation can also activate PI3K/protein kinase B (AKT)/endothelial nitric oxide synthase (eNOS)/mammalian target of rapamycin (mTOR) pathway in endothelial cells to enhance cardiomyogenesis. Another pathway that is activated after ligand-binding to OXTR-mediated opening of Ca²⁺ channels involve free Gβγ subunits. This can activate afterwards Ras, Raf-1, MEK1/2 or ERK1/2, which then can activate certain transcription factors, such as COX-2, or c-fos, linked with Oxt biological functions including regulation of prostaglandin secretion, labor and parturition, social behavior, and vascular function, among others. Gαi and Gαs can activate both the adenylate cyclase (AC) pathway. AC when activated transforms adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), second messenger which is converted to protein kinase A (PKA), inducing then cellular responses including cardiovascular and reproductive function. Finally, Oxt can also bind and act through transient receptor potential vanilloid (TRPV), which for instance can activate MAPK1/2 signaling, inducing in last term actions such as anxiolytic effects. Overall, these cascades transduce in downstream signaling of diverse transcription factors, such as cAMP response element-binding protein (CREB), myocyte enhancer factor-2 (MEF2), transcriptional coactivator CREB-regulated transcription coactivator (CRTC) to induce Oxt-mediated actions, such as anxiolytic effects. The question mark represents the knowledge gap on the Oxt signaling involved in the regulation of eating behavior. Informed by existing findings and figures from literature.^{2,28,32–34}

TABLE 1 Studies investigating the effects of microbiota on central and peripheral oxytocin neuropeptide levels.

Context	Species	Microbiota-targeted intervention	Outcome		Reference
			Oxytocin	Overall	
Social behavior	Mice	Ab cocktail (PD21 onwards).	Reduction in Oxt mRNA in HYP of stress mice.	Reduction in anxiety and cognitive deficits.	53
	Mice	Ab cocktail (PD21 onwards) or GF.	Downregulation of Oxtr PFC and a trend for upregulation of Oxt in HYP, in Ab-treated mice. No significant differences in GF mice.	Disruption of signaling pathways involved in social behavior and pain regulation.	54
	Rats	GF or CONV animals.	Increased OXTR protein levels in cingulate, prelimbic, lateral/medial/ventral orbital cortex, and septum across all ages in male, but not female.	Ontogenic study with findings potentially important in neurodevelopment.	55
Disease Model/Disorder Model					
	Mice (AD model)	Ab cocktail (PD21-PD100).	Increased central OXT protein levels in control mice.	Decreased anxiety- but not depression-like behaviors (Ab-treated mice) but no alterations in HPA axis function.	56
	Mice (MHFD model)	<i>L. reuteri</i> MM4-1A (ATCC-PTA-6475) and <i>L. johnsonii</i> (ATCC 33200) (1×10^8 organisms/mouse/day for 4 W).	Increased Oxt immunoreactivity in PVN of MHFD mice.	Reversed social deficits in MHFD offspring.	14
	Mice (ASD model)	<i>L. reuteri</i> MM4-1A (ATCC-PTA-6475) ($\sim 1 \times 10^8$ organisms/mouse/day daily for 4 W).	Reduced Oxt ⁺ neurons in PVN of Shank3B ^{-/-} mice.	Rescued social deficits and interaction in ASD model, in a dependent manner on oxytocinergic and dopaminergic reward systems.	17
	Mice (ASD model)	<i>Blautia stercoris</i> MRx0006 (1.0×10^9 CFU/200 μ L/day for 3 W).	Upregulation of Oxt and Avp in HYP of BTBR mice.	Improvement in social deficits and anxiety-like behavior.	19
	Mice (ASD model)	<i>L. reuteri</i> ATCC MM4-1A (ATCC-PTA-6475) (1×10^9 CFU/200 μ L PBS/day for 3 W).	Upregulation of Oxt in HYP of Shank3 KO male mice, whereas Oxt HYP was downregulated in female.	Attenuated non-social behaviors in male and reduced repetitive behaviors in both female and male mice.	57
	Rats (ASD model)	<i>Lactobacillus helveticus</i> CCFM1076, <i>L. acidophilus</i> La28 and <i>L. acidophilus</i> JCM 1132 (1×10^9 CFU/rat/day for 4 W).	Only <i>L. helveticus</i> CCFM1076 increased Oxt synthesis in HYP of VPA-treated rats.	Amelioration of ASD-like behaviors.	58
	Humans (with ASD)	<i>L. plantarum</i> PS128 (2 capsules/day of 6×10^{10} CFUs for 28 W) together with Oxt administration (1 puff of 4 IU/day in 1st W of the 2nd stage, 1 puff per nostril daily (8 IU/d) for the 2nd W, 1 puff per nostril twice a day (16 IU/d) for the 3rd W, finally, 2 puffs per nostril twice a day (32 IU daily) for the 4th W).	No significant changes in serum Oxt levels in the 3 treatments compared to placebo groups.	Improvements in ASD-like behaviors.	59

TABLE 1 (Continued)

Context	Species	Microbiota-targeted intervention	Outcome		Reference
			Oxytocin	Overall	
Eating behavior	Humans	Multiprobiotic: <i>L. acidophilus</i> (1.8×10^9 CFU/capsule), <i>B. bifidum</i> (1.8×10^9 CFU/capsule), <i>B. lactis</i> (1.8×10^9 CFU/capsule), <i>B. longum</i> (1.8×10^9 CFU/capsule), <i>L. rhamnosus</i> (1×10^9 CFU/capsule), <i>L. reuteri</i> (2 capsules/ day, where 1×10^9 CFU/capsule for 12 W).	Increased serum levels Oxt.	Improvement in eating behavior and metabolic status.	20
Metabolism	Mice	<i>L. reuteri</i> 2546 (4, 6 or 8 W in C57BL/6 WT and 8 W in Oxt-KO B6 and 129S-OxTtm1Wsy/J mice)	Increased plasma Oxt levels and Oxt-dependent BW.	Decrease in BW and lower risk for obesity.	15
Wound healing	Mice	<i>L. reuteri</i> [ATCC-PTA-6475] (3.5×10^5 CFU/ mouse/day; drinking water for 2 W in C57BL/6 WT, 2–3 W for Oxt-KO and Oxt-WT)	Upregulation of plasma Oxt levels.	Enhancement of wound-healing properties	12
	Mice	<i>L. reuteri</i> ATCC-PTA-6475 ($3.5\text{--}5.5 \times 10^5$ CFU/mouse day for 4 W).	Increased plasma Oxt levels and in Oxt-producing cells in the caudal PVN and decreased plasma corticosterone levels.	Skin wound repair benefits, including capacity, and increased in epidermal closure speed.	13

Note: Studies classified firstly by context, specie, microbiota-targeted intervention (i.e., microbiota depletion by antibiotic cocktail, germ free, or probiotic treatment), outcomes according to effects on oxytocin (levels or signaling) and the respective reference.

Abbreviations: Ab, antibiotic; AD, Alzheimer's disease; ASD, autism spectrum disorder; CFU, colony forming units; CONV, conventional; GF, germ-free; HPC, Hippocampus; HYP, hypothalamus; KO, knock-out; MHFD, maternal high-fat diet; NTS, nucleus tractus solitarius; Oxt, oxytocin; OxtR, oxytocin receptor; PD, postnatal day; PFC, prefrontal cortex; PVN, paraventricular nucleus; SC, subcutaneous injection; VPA, valproic acid; W, week; WT, wild-type.

2.4 | Challenges with measuring oxytocin

As has been introduced, Oxt is produced both in the brain and the periphery. It is currently unknown whether plasma Oxt levels correlate with central Oxt release and whether peripheral administration can increase central Oxt levels because Oxt cannot readily cross the blood-brain barrier (BBB).⁶⁶ Recently, it was suggested that Oxt may reach the brain through transportation via the receptor for advanced glycation end products (RAGE) which is expressed in endothelial cells at the BBB.^{67,68} RAGE receptors have been shown to be crucial for the effect of exogenous Oxt on social behavior, such as bonding and parenting.^{67,68} One additional difficulty in studying Oxt levels in preclinical and especially clinical trials is the poor performance of Oxt enzyme-linked immunoassays (ELISAs) that yield highly variable, inconsistent, and uncorrelated results even for the same sample.^{69–72} Furthermore, Oxt has a short half-life (around 4–6 min),^{73,74} is broken down by tissue proteases and binds to plasma proteins which makes the quantification of Oxt levels, particularly in plasma, challenging. Thus, the field would benefit from novel detection methods enabling accurately determine how (microbiome-targeting) interventions modify Oxt levels across the gut-brain axis.

3 | PHYSIOLOGICAL FUNCTIONS OF OXYTOCIN AND EFFECTS OF THE MICROBIOTA

Oxt was originally discovered for its effects on peripheral tissues, most importantly female reproductive organs, where it induces uterus contractions during labor, and mammary glands, where it contributes to lactation. Importantly, Oxt also affects the function of adipocytes,^{6,75} pancreatic β cells⁷⁶ and the GI tract.^{63,77} These all produce hormones and other nutrient-related signals that influence food intake.

Since the late 1970s, Oxt has also been investigated as a neurotransmitter or neuromodulator with important effects on reproductive behavior.⁷⁸ For example, Oxt has been shown to play a role in maternal attachment,⁷⁹ the onset of maternal behavior,⁸⁰ sexual responsiveness^{81,82} and mating behaviors.^{82,83} Further, Oxt modulates memory functions,^{84,85} and olfactory sensory perception.⁸⁶ The mechanism of these physiological actions is thought to involve interactions between the central oxytocinergic, dopaminergic, serotonergic^{87–89} and the endogenous opioid system.⁹⁰ However, further research is needed to further understand the precise underlying signaling pathways.

The focus of the review is to discuss the potential impact of the microbiota on Oxt's role in the central regulation of food intake

behavior (Section 4), but microbiota-mediated changes in Oxt in the context of sociability (Section 3.1) and stress (Section 3.2) also need to be considered, as they can subsequently lead to altered homeostatic and hedonic eating. For example, stress increases food intake particularly of sweet carbohydrate-rich foods^{91–93} and food intake increases when consumed in a group environment.^{94,95} The role of the microbiome in the neurobiology of social behavior and social stress has been reviewed in detail elsewhere.⁹⁶ We focus on the potential link with Oxt and the relevance of the gut microbiota-oxytocin-behavior triad in modulating eating behavior.

3.1 | Oxytocin, the microbiome, and social behavior

Oxt is considered a prosocial hormone⁹⁷ as it has been shown to influence social behaviors such as, social recognition and attention,⁸⁶ social motivation and perception,⁷⁹ social cognition,⁹⁸ social memory,⁹⁹ as well as short- and long-term effects in social bonding.^{100–102} For instance, intranasal Oxt is associated with antiaggressive behavior in male rats after acute and repeated administration. These animals displayed increased sociability toward an unfamiliar intruder and reduced offensive aggression. In addition to which they had strengthened social bonding towards a female partner.¹⁰³ Moreover, Oxt also influences reward processes such as social reward and food reward mechanisms.^{4,5,104,105} Recent preclinical studies demonstrated that Oxt interacts with numerous brain regions involved in sociability, including the orbital frontal cortex, anterior cingulate cortex, and prefrontal cortex (PFC) to exert prosocial effects, and regions involved in the mesocorticolimbic dopamine system (i.e., the ventral tegmental area (VTA), substantia nigra, striatum) (see Figure 3).^{7,106,107} Specifically, Oxt has been shown to activate VTA neurons leading to increased dopaminergic activity in the mesocorticolimbic system.⁷ Furthermore, Oxt release in VTA appears to be necessary in order to evoke social reward.⁷ Oxt also displays potent anxiolytic effects.^{107,108} It is suggested that this is mediated by modification of serotonergic signaling.¹⁰⁸ However, despite the overwhelmingly prosocial effects documented in these studies, other reports suggest that the action of Oxt is dependent upon a prosocial environment during administration and there are a lot of unknowns regarding factors that affect an individual's response.¹⁰⁹

The microbiota has been shown to affect social behaviors and overall mental health in preclinical and clinical studies in rodents and humans which has led to the term “psychobiotics”.^{110,111} Although many of these studies have not specifically investigated the involvement of Oxt (see all the studies found linking microbiota with Oxt in Table 1), one study suggests that antibiotic-treated mice show reduced anxiety-like behavior and a concomitant increased OXT protein expression levels in the brain⁵⁶ (further details in Table 1). Additional studies have investigated the possible contribution of Oxt to the beneficial effects of microbiome-targeting interventions in the context of social behavior, most of which were performed in disease models (Table 1). Recent studies highlight that a dysregulation of Oxt and single nucleotide polymorphisms (SNPs) or epigenetic

modification of the *Oxtr* gene contribute to the neurobiology and pathophysiology of certain neuropsychiatric disorders, including autism spectrum disorder (ASD),^{17,112,113} schizophrenia,^{114,115} anxiety disorders,¹¹⁶ depression,¹¹⁷ obsessive compulsive disorder¹¹⁸ and eating disorders.¹¹⁹ Moreover, microbiome-targeting interventions may be able to correct these deficits.¹²⁰ For instance, certain studies suggested that patients with ASD have significantly lower Oxt circulating levels compared to a control population,^{113,121} even though opposite results have also been described.^{122,123} Oxt administration, in turn, has been shown to reduce autistic-like behaviors¹²⁴; although the data are not consistent in human trials.¹²⁵ At the level of the brain, Oxt administration enhances functional connectivity between the ventral PFC and striatum,¹²⁶ which suggests that the mesocorticolimbic system is potentially involved in this Oxt-mediated effects on ASD. Microbiome-targeting strategies such as administration of *Blautia stercoris* MRx0006 ameliorate autistic-like behavior and increase OXT protein levels and Oxt expression in the hypothalamus, in genetic mouse models of ASD (Shank3B^{−/−})¹⁹ (see Table 1). Administration of *L. reuteri* MM4-1A to Shank3B^{−/−} mice restored social interaction and VTA plasticity, effects which were prevented in mice lacking the *Oxtr* in dopaminergic neurons.¹⁷ In humans, administration of probiotic *Lactiplantibacillus plantarum* PS128 and Oxt had a synergistic positive effect on social and behavioral scores in ASD patients which was associated with changes in the gut microbiota composition⁵⁹ (further details in Table 1). A microbiota-Oxt link has also been suggested in schizophrenia, which is another disorder where sociability is affected and where microbiome-targeting interventions have shown benefits. It has been shown that Oxt levels in the cerebrospinal fluid are higher in patients with schizophrenia compared to controls.¹²⁷ In contrast, serum Oxt levels appear to be lower, indicating that peripheral and central levels of Oxt may be differentially regulated and have divergent effects which need to be further investigated.¹²⁷ Increased Oxt levels, however, are thought to improve schizophrenia behaviors and symptoms.¹²⁸ Preliminary data suggests that probiotic administration may improve symptomatology and comorbidity in patients with schizophrenia, however, the extent to which such microbiota-targeted strategies involve Oxt remains to be investigated.^{129,130}

Accordingly, microbiota seems to impact host Oxt and Oxt signaling, but recent evidence points towards a modulation of the gut microbiota by this neuropeptide. A recent study shows alterations in gut microbiota composition after Oxt administration. In the study by Dangoor et al.¹¹ Oxt administration led to altered gut microbiota diversity, which was linked with a decrease in anxiety- and depression-like behaviors in a corticosterone (CORT)-induced stress rat model.¹¹

Many of the behavioral disorders including ASD and schizophrenia are also characterized by impaired stress responses, and both microbiome-targeting interventions and Oxt administration have been shown to have potential to ameliorate the behavioral deficits associated with these neurodevelopmental disorders.^{131–134} Stress not only impacts social or anxiety-like behaviors, which is relevant in the aforementioned disorders,^{135,136} but also plays a key role in the regulation of food intake behaviors^{91,137–139} (see studies on stress, food intake and their link to Oxt in Section 4.3).

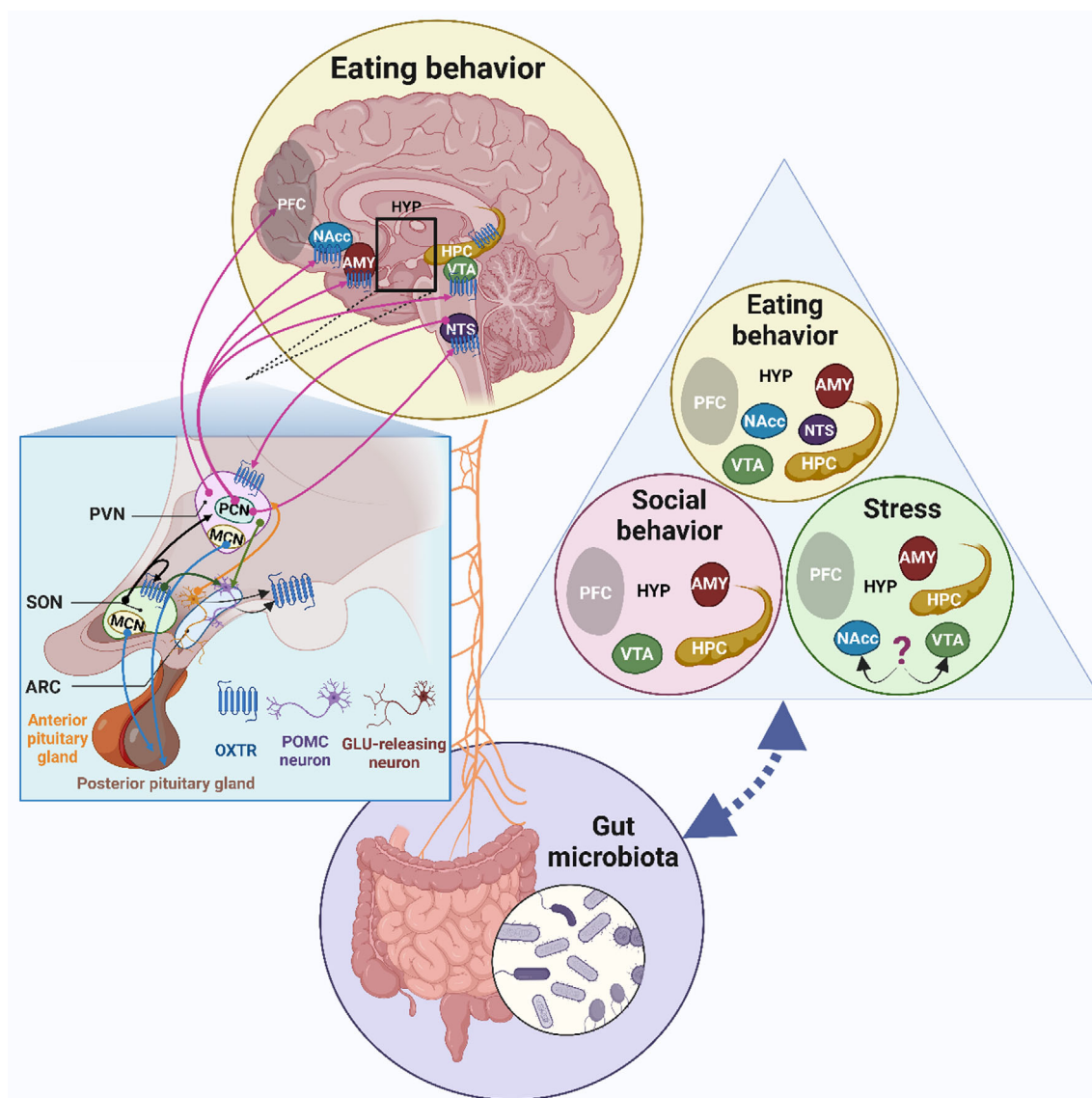


FIGURE 3 Overview of the brain regions involved in oxytocin's effects on eating behavior, social behavior and stress and potential interaction of the gut microbiota as a key player. Oxytocin (Oxt) is a neuropeptide that is produced in magnocellular neurons (MCN) located in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus (HYP) as well as in parvocellular neurons (PCN) located in the PVN (blue box). After Oxt synthesis in MCN within the PVN and PON, the neuropeptide is transported along axons to the posterior pituitary gland (brown, blue arrows), from where is released into the bloodstream. The brain regions with oxytocinergic signaling involved in regulating eating behavior are shown in the yellow circle and blue box, social behavior in the red circle and stress in the green circle. In the HYP (blue box), there is a complex interaction of Oxt-producing and Oxt receptors (OXTR) expressing cells in different nuclei. Glutamatergic neurons (GLU) in the arcuate nucleus (ARC, blue region) express OXTR and project to neurons in the PVN (orange arrow) to regulate Oxt secretion and enhance satiation through modulation of proopiomelanocortin (POMC) neurons. Oxt from PVN and SON also modulate the activity of these OXTR-expressing POMC neurons in the ARC (green arrows), which also induces satiation. Oxt released from MCN in the SON can also regulate Oxt secretion in the SON itself and in the PVN in an autocrine manner. Oxytocinergic neurons from the PVN (pink lines) project to many other brain regions (pink arrows) that are involved in the control of eating behavior including the nucleus tractus solitarius (NTS), the ventral tegmental area (VTA), the hippocampus (HPC), the amygdala (AMY), the nucleus accumbens (NAcc), and the prefrontal cortex (PFC). These brain regions with Oxt neurocircuitry have been also shown to be involved in the control of stress (green circle) and social behaviors (pink/red circle). As discussed in the review, the gut microbiota (purple circle) has been linked (blue arrows) with stress, eating behavior and Oxt independently, but also with Oxt particularly in social behavior context (the three effects are represented within a pyramid). The vagus nerve (in orange) connects the gut and the brain via gut-brain axis and is one mechanism by which gut microbiota is suggested to regulate appetite, eating and social behavior and stress. The question mark shows the brain regions suggested to be involved in oxytocinergic neurocircuitry-linked to stress regulation but that are not demonstrated yet.

Therefore, it is likely that Oxt-mediated effects on stress responses will have converging effects on sociability, anxiety as well as eating behavior.

3.2 | Oxytocin, the microbiome, and stress

Stress is defined as physiological response to a potentially harmful stimulus and leads to the activation of the hypothalamus-pituitary-adrenal axis (HPA) and the sympathetic nervous system. High Oxt levels are associated with an attenuated stress response,^{140–142} which may protect against the detrimental effects of stress and signify an improved stress-resilience. It is suggested that Oxt release within the hypothalamus directly modulates corticotropin-releasing hormone (CRH) expression leading to reduced cortisol levels and the activity of presynaptic neurons that project to sympathetic efferents in the medulla.^{143,144} These regulate sympathetic output^{143,144} and Oxt has been shown to reduce heart rate and blood pressure.^{145,146} In addition, Oxt might also reduce the sensitivity to stressful stimuli by reducing amygdala activity.¹⁴⁷ Moreover, chronic ICV Oxt injection at low dose (1 ng/h for 15 days) exerted protective effects against stress and anxiety, whereas high dose (10 ng/h) was detrimental with anxiogenic effects in mice.¹⁴⁸

The composition of the microbiome modulates the response to acute^{149,150} and chronic stress.¹⁵¹ GF mice showed hyperresponsiveness in the HPA axis after restraint stress, which was accompanied elevated serum levels of corticosterone.^{152,153} On the contrary, microbiome-targeting interventions have been shown to improve the stress response. For example, administration of the probiotic *L. plantarum* 299v¹⁵⁴ decreases stress-induced cortisol levels in humans. In addition, a reduction in cortisol awakening responses was observed in healthy obese adults following administration of the probiotic *B. longum* APC1472.¹⁵⁵ Furthermore, *B. longum* APC1472 also reduced the plasma corticosterone levels in high-fat diet (HFD) mice.¹⁵⁵ The contribution of Oxt signaling has been studied in a limited number some of these studies. Desbonnet et al. (2015) found that although stress-induced cortisol levels were not different between antibiotic-treated and control animals, Oxt levels were higher in the stressed control group compared to stressed antibiotic-treated animals suggesting that an intact microbiota is required to trigger stress-induced Oxt expression.⁵³ It is tempting to speculate that modulation of Oxt levels also contributes to the beneficial effects of probiotics on stress responses (Figure 3, green circle).

4 | EATING BEHAVIOR, OXYTOCIN AND THE MICROBIOME

Homeostatic food intake is regulated in the hypothalamus particularly the arcuate nucleus (ARC) of the hypothalamus where two sets of antagonistic cell types increase (orexigenic AgRP/NPY neurons) or decrease (anorexigenic POMC neurons) appetite and food intake.^{156–158} However, the complex neurobiology and neurocircuitry that is involved in the full control of eating behavior can be classified according to the homeostatic and non-homeostatic regulation.^{159,160}

Homeostatic regulation comprises the control of metabolic and energy status, mainly via the hypothalamus and brainstem nuclei (Section 4.1) whereas non-homeostatic regulation involves motivation, hedonic eating learning, memory, and cognitive aspects of feeding, which are controlled by high-order brain regions, including the hippocampus, the mesolimbic system, and the frontal cortex (Section 4.2).^{156,158} Even though this classification is made, the same peripheral signals, such as gut hormones and microbiota-derived metabolites, can converge on both systems, for instance via the vagus nerve signaling, blood circulation or other direct and indirect brain signaling mechanism.^{157,161}

Stress also influences food intake in a bidirectional way.^{91–93} For example, consumption of highly palatable food increases CORT levels and stress increases food cravings.^{138,162} Thus, in addition to affecting food intake by itself, Oxt and the microbiota may also contribute in part by modifying social behavior and stress levels (see Section 3.1 and 3.2).

4.1 | Oxytocin and homeostatic appetite regulation: A role for the microbiome?

The hypothalamus is the main brain region involved in the homeostatic control of food intake. The activity of orexigenic AgRP/NPY and anorexigenic POMC neurons is regulated by signals from the periphery. This includes signals from the brainstem, specifically the nucleus tractus solitarius (NTS), which receives information about the status of the periphery via the vagus nerve and spinal afferents, as well as circulating metabolites and hormones (leptin, Glp-1, ghrelin, CCK).^{5,156,157,161,163} Importantly, there is a bidirectional communication between hypothalamic centers regulating food intake (ARC) and Oxt-producing parvo- and magnocellular cells in the PVN (Figure 3, blue box). Not only will Oxt secretion modulate the activity of ARC neurons, but POMC and AgRP/NPY neurons also increase and decrease Oxt secretion, respectively.^{164,165}

Oxt's role in regulating food intake is incompletely understood. Food intake stimulates oxytocinergic neurons, which would suggest an anorexigenic mode of action for Oxt. Indeed, many preclinical studies have demonstrated that ICV as well as IP injection of Oxt reduced food intake in different animal models, such as rats, mice, and monkeys (Supporting Information, Table 1).^{166,167} This is associated with an increase in c-Fos expression in cells in the NTS,¹⁶⁸ and a vagus-dependent activation of c-Fos in hypothalamic Oxt neurons at a molecular level.¹⁶⁹ In contrast, Oxt-KO animals display an increased preference for palatable and sugary food.^{9,170} However, in humans, high Oxt levels are observed in obese individuals^{6,171} and intranasal Oxt administration has shown conflicting results with regard to food intake^{4,8,105,172–174} (see further details in Supporting Information, Table 1). An additional mechanism by which Oxt might regulate food intake behavior, includes the modification of signaling pathways from other food intake-regulating hormones. Our laboratory has shown that an OXTR-ghrelin receptor (GHSR) heterocomplex reduces GHSR receptor signaling, but it is currently unknown whether this modulates food intake.¹⁷⁵

The gut microbiota has extensively been investigated for its role in host metabolism,^{155,176,177} eating behavior and appetite,^{178–181} and

is associated with metabolic disorders (see Supporting Information, Table 2).^{50,176,177,182–184} GF mice consume more food than their CONV counterparts which is associated with higher expression of orexigenic *Npy* and *Agrp* and lower expression of anorexigenic *Pomc* in the hypothalamus.¹⁸¹ In the brainstem, expression of *Bdnf* and *Glp-1* (both considered as anorexigenic neuropeptides) are higher in GF compared to CONV mice.¹⁸¹ The effects of antibiotic treatment on food intake are inconsistent between studies and may be dependent upon the antibiotic regime, the complete or incomplete depletion of the microbiota, as well as other factors such as sex and age.

It is suggested that a direct impact of bacteria-derived metabolites, such as the short-chain-fatty acids (SCFAs), amino acids or bile acids⁴⁸ and hormones produced by the microbiota (GABA, serotonin, 5-HT) may act on central neurocircuitry through the vagus nerve, as one mechanism by which the gut microbiota regulates appetite and eating behavior. Administration of the SCFA butyrate for example, decreases food intake and reduces c-FOS expression in orexigenic NPY neurons in a vagus nerve-dependent manner. Serotonin (5-HT) derived dietary tryptophan and GABA derived from glutamate are both generated by the microbiota and have been shown to reduce appetite regulation via gut-brain signaling and secretion of appetite-linked hormones, such as cholecystokinin (CCK).¹⁸⁵ In addition to such mechanistic studies, there is ample evidence that microbiome-targeting interventions (prebiotics, probiotics) modulate food intake and hypothalamic gene expression (see Supporting Information, Table 2). For instance, administration of prebiotics, such as oligofructose was shown to prevent the increase in food intake, and body-weight associated with HFD¹⁸⁶ (see Supporting Information, Table 2). On the contrary, supplementation with *Lactocaseibacillus rhamnosus*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum* was associated with a reduction in food intake and bodyweight as well as improvements in leptin and insulin resistance in the hypothalamus of mice¹⁸⁷ (see Supporting Information, Table 2).

As previously described, the gut microbiota has been demonstrated to modulate Oxt expression (Section 2.3), but it is currently unknown whether this relates to homeostatic control of food intake and eating behavior. Given the evidence presented above, it seems likely that Oxt is involved in the effects of at least some microbiome-targeting interventions. Indeed, a recent study by Narmaki et al.²⁰ demonstrated that supplementation with a multistrain probiotic increased circulating Oxt levels in obese women with food addiction and decreased in serum leptin and NPY levels.²⁰ Consequently, this improved eating behavior and reduced food intake.⁷¹ Further research is needed to better understand this potential crosstalk between microbiota, Oxt and food intake, both centrally and peripherally.

4.2 | Beyond homeostatic appetite regulation: A microbiota-gut-oxytocin pathway?

Non-homeostatic regulation of eating behavior and food reward involves frontal cortical regions (PFC, orbitofrontal cortex (OFC), and insula), the mesolimbic system (VTA and nucleus accumbens [NAcc])

and the hippocampus. These brain regions are involved in regulate impulsivity, reward, memory, and sociability.

The PFC is thought to inhibit impulsive eating behavior except for a certain subset of neurons in ventral medial PFC (vmPFC).^{158,188} Petrovich et al. (2007) demonstrated that an intact vmPFC is required to induce eating in sated rats whereas sated rats with a lesion of the vmPFC consume less food than control rats suggesting that this region is necessary for controlling eating responses.¹⁸⁸ Both the OFC and insula are involved in the coordination of perception of palatable foods, which increases motivation towards food.^{156,158} It is suggested that these effects demonstrated in rodents might translate to humans since hunger activates similar cortical regions across species.¹⁸⁹ The mesolimbic dopamine pathways (comprising the VTA and the NAcc) encode food reward processes which enhance food consumption^{158,159,190} and thus, can override signals from homeostatic systems, such as the hypothalamus^{158,159} but also gut hormones signals.^{158,190} Lastly, the hippocampus is a brain region that contributes to the regulation of food intake by integrating memory cues, learning, visual, spatial environment information, and energy status.^{158,159,190,191} The ventral hippocampus in particular has been shown to be involved in the regulation of palatability and food preference through receiving endocrine signals and transferring these signals to higher-brain regions such as the NAcc.¹⁹²

Oxytocinergic neurons project into many of the brain regions that were described above (Figure 3)^{30,193} and thus, may regulate food intake through modulation of these areas. However, to date, our understanding of the underlying neurocircuitry is limited. Oxt neurons in the PVN have been shown to activate dopaminergic neurons in the NAcc and VTA,^{5,194,195} which is essential for reward-driven social behaviors.¹⁹⁶ Exogenous administration of Oxt into the CNS of different animal models, specifically injection into the NAcc⁹⁴ and VTA,¹⁹⁴ decreases sucrose intake after food deprivation¹⁹⁷ and the consumption of fructose-sweetened beverages¹⁶⁶ (see Supporting Information, Table 1). Another study confirmed this finding on food intake in a non-social context, but also that found that Oxt injection was not able to inhibit food intake when rats were presented food in social setting.⁹⁴ The same research group demonstrated that administration of the OXTR antagonist L-368,899 increases sugar intake independently of social status as it increased sugar intake in both subordinate and dominant mice¹⁹⁸ (see Supporting Information, Table 1). These effects are ascribed to changes in the perceived reward and food palatability^{5,104,194} and have been replicated in human trials. Intranasal Oxt administration, for instance, was found to reduce reward-driven eating of palatable food such as chocolate cookies.⁴ Furthermore, Oxt has been linked with food choice,¹⁹⁹ cognitive control of food cravings¹⁷⁴ and the processing of food-reward value¹⁰⁵ (see Supporting Information, Table 1). In this line, Olszewski et al.¹⁹⁹ demonstrated that the OXTR antagonist L-368,899 induced a preference towards sugar intake compared to either sucrose alone or in combination with lipids in mice, which was accompanied by increased c-Fos immunoreactivity in brain regions linked with reward, satiety and aversion¹⁹⁹ (see Supporting Information, Table 1). This research group also demonstrated that L-368,899 also increases carbohydrate (sucrose, glucose, fructose,

polycose, or corn starch) compared to noncarbohydrate intake. This was accompanied by an upregulation of the expression of *Oxt* gene in hypothalamus of mice with sucrose and corn starch intake.²⁰⁰

Although the gut microbiota is known to modulate PFC-regulated behaviors (including social and anxiety-linked behaviors),^{201,202} reward signaling²⁰³ and hippocampal function,²⁰⁴ our understanding of the subsequent effects on food intake and eating behavior is currently limited. These regions, and particularly the PFC, however, are closely interlinked with brain regions that regulate food intake (Figure 3) which suggest that microbiome-targeting interventions may affect food intake through modulating these regions.^{158,205} For instance, *L. rhamnosus* supplementation to CONV-R mice downregulated GABA_A-α2 receptor gene expression in PFC, which was linked with a reduction in depression- and anxiety-like behaviors mediated by the vagus nerve²⁰⁶ (see Supporting Information, Table 2). Fecal microbiota transplant (FMT) from obese mice modulated gene expression and learning in PFC of recipient mice suggesting that the microbiota affects feeding-linked cognition in the PFC²⁰⁷ (see Supporting Information, Table 2). The gut microbiota has been shown to modulate reward signaling.²⁰³ It has been shown that GF compared to CONV animals have increased synthesizing dopaminergic turnover (DOPAC/dopamine ratio).^{203,208,209} Moreover, GF mice display an increase in dopamine D1 receptor expression in the hippocampus, which was decreased in striatum and NAcc. No significant differences in D2 receptor expression in these brain regions were detected when GF mice were compared to specific pathogen free (SPF) mice.²¹⁰ Thus, highlighting an implication of the microbiome on brain regions involved in reward processes and DA signaling, which is critical on cognitive and reward functions, as well. Control mice consuming the prebiotic fructo-oligosaccharides (FOS) have increased food intake and preference towards palatable food. However, FOS administration reduced overall food intake and preference for palatable food when given together with control chow diet to mice previously exposed to high-fat high-sugar (HFHS) diet.¹⁷⁹ This was associated with a trend for increased expression of dopamine-associated genes in the NAcc and, increased expression of the orexigenic *Agrp* and *Npy* in the hypothalamus.¹⁷⁹ Additionally, mice receiving FMT from obese animals displayed increased sensitivity to the effects of a HFHS diet compared to those receiving FMT from lean mice. This included a higher food reward and changes on the expression of dopaminergic genes in the striatum.¹⁷⁸ In humans, administration of the SCFA propionate, via colonic delivery, reduced the appeal of high energy food pictures suggesting that colonic propionate might play a role in the attenuation of reward-context eating behavior.²¹¹ Effects of the microbiota on the hippocampus have previously been investigated because of its involvement in memory function. It has been shown that the microbiota affects neurogenesis,²¹² structure,²¹³ physiology,²¹⁴ gene expression²¹⁵ and neurotransmitter levels.²¹⁶ Antibiotic-treated, GF and probiotic-supplemented mice have shown alterations in memory function and related behavior, but there is currently no evidence that this in turn affects eating behavior.¹⁹¹ A recent preclinical study has shown however that a high-dose administration of the probiotic-mix VSL#3 prevented diet-induced memory deficits on a place task in a dependent manner of hippocampus, even

though this exposure did not alter energy intake or bodyweight.²¹⁷ Accordingly, the hippocampus is linked with episodic memory, which has been shown to modulate food intake in humans.^{158,218} This overall suggests that a potential effect of gut microbiota on hippocampal-driven regulation of food intake warrants investigation.

4.3 | Eating behavior, stress, and oxytocin

Stress alters metabolic needs and the function of many higher brain regions involved in the regulation of food intake. Further, brain regions involved in the regulation of stress responses are in close anatomical proximity to those regulating food intake. For example, in the hypothalamus which ensures that metabolic demands and energy status are adjusted during stressful events.²¹⁹ On the one hand, the intake of highly palatable or carbohydrate-based food reduces stress-induced glucocorticoid release and stress perception.^{219–221} On the other hand, stress modulates the amount and composition of food that is consumed. Acute stress, for example, suppresses food intake and increases energy expenditure,^{219,222} whereas perceived stress has been shown to increase intake of palatable high-fat/high-carbohydrate food.^{219,220,223}

The exact mechanisms that link food intake and stress response are not completely understood yet, but it is thought to involve a direct crosstalk between orexigenic AgRP/NPY neurons in the ARC and CRH-releasing neurons in the PVN. In addition, appetite-linked hormones ghrelin and leptin might be involved. In mice, activation of CRH neurons enhances food preference towards a high-carbohydrate diet.²²⁴ In line with this finding, glucocorticoid intake in humans leads to an increase in food intake and a higher preference for palatable carbohydrate-rich food²²⁵ suggesting a modulation of the orexigenic AgRP/NPY neurons and reward-driven processes. Inhibition of the glucocorticoid receptor, CRHR1 was able to reduce stress-induced food consumption and food cravings in humans.²²⁶ Additionally, the orexigenic hormone ghrelin has been shown to enhance stress responses in rodent, whereas the anorexigenic hormone leptin, inhibits the release of noradrenaline and adrenocorticotrophic from PVN under stressful stimulus.²²⁷

As previously mentioned, *Oxt* is also produced in the hypothalamus³ and can affect the bidirectional communication between stress and food intake centers.^{5,156,167,219,220} Both food intake and stressful stimuli activate *Oxt* neurons^{169,219} which is linked to a modulation of downstream responses in brain regions involved in the regulation of reward, cognition, emotion, and homeostasis.^{71,219} In addition, manipulation of *Oxt* in the brain has been shown to modulate both stress responses and food intake (SI, Table 3). In a preclinical setting, Barrett et al.²²⁸ showed that intraparenchymal thalamus (PVT) *Oxt* injection in female and male mice attenuated stress- and anxiety-induced hypophagia but did not alter food intake under normal conditions.²²⁸ In addition, *Oxt* administration increased the number of active lever presses suggesting increased motivation and learnt food reward behavior which were inhibited when animals were treated with the OXTR antagonist, atosiban.²²⁸ In humans (both obese and normal weight men), *Oxt* administration was able to reduce stress-induced

HPA activation and inhibits hunger-induced food intake, but only in obese males²²⁹ (see all the studies found linking Oxt and stress in context of food intake/eating behavior in Supporting Information, Table 3). Further, genetic polymorphisms of OXTR have been linked with higher vulnerability to stressful stimuli and an aggravation of symptomatology, including behavioral,²³⁰ of eating disorders, such as AN¹¹⁹ or overeating²³¹ in humans (also see section 4.4).

Whilst it has been shown individually that the microbiota affects Oxt, stress and food intake, it is currently unknown how the microbiota affects this triad. Evidence suggest that Oxt might be an important player especially because, in addition to the brain, Oxt is expressed in enteric neurons (see section 2) which are more closely located to the intestinal microbiota and may regulate food intake and stress responses in the hypothalamus via vagal afferents.

4.4 | Considerations for weight management, energy balance and dysregulation of food intake

In this review, we have so far concentrated on evidence linking Oxt and eating behavior under normal conditions. Modulation of Oxt has, however, also been suggested as a novel treatment strategy in multiple eating disorders such as anorexia nervosa (AN), binge-eating, bulimia nervosa (BN) and obesity.^{156,158}

Individuals with AN, but not BN, display lower plasma Oxt levels compared to healthy controls.²³² In contrast, food-induced Oxt responses were higher in individuals with AN.²³³ It is suggested that this increase is related to the food-related stress response in individuals with AN.²³⁴ Intranasal Oxt administration has shown beneficial effects in individuals with AN and was associated with a decrease in attentional vigilance and eating-related concern as well as a reduction in salivary cortisol levels which overall points to a potential beneficial effect of Oxt in this disorder^{219,235,236} which is likely because of its holistic effects on food intake regulation, mood, stress response, memory function and sociability.

With regard to obesity and metabolic syndrome, increased levels of plasma Oxt have been reported in both women and men.¹⁷¹ However, the opposite has also been found. Serum Oxt levels negatively correlated with body mass index (BMI), waist circumference and waist-to-hip-ratio.²³⁷ The therapeutic effects of Oxt administration in obesity and metabolic syndrome are currently under investigation⁷⁰ to assess dosage, administration regime, efficacy, and safety of such treatments.

Given differences in the microbiome composition between lean and obese individuals and changes of microbiome composition associated with dietary interventions,¹⁸³ microbiome-targeting interventions have been discussed as an additive therapeutic approach for obesity.^{183,238} Indeed, preclinical and clinical studies suggest that probiotics can reduce bodyweight in obese rodents and humans,²³⁸ but manipulation of the gut microbiota alone might not be sufficient or effective enough to alter bodyweight.¹⁸³ To date, the precise mechanisms of the gut microbiota action are unknown and only few studies addressed effects on food intake and energy expenditure, particularly in humans. In mice, a reduction of bodyweight by administration of

Hafnia alvei HA4597, was associated with reduced food intake in ob/ob mice (3×10^8 CFU/day, 18 days), but not high-fat diet-induced obese mice (4×10^7 CFU/day, 46 days).²³⁹ In humans, it was recently shown that a *Hafnia alvei* strain improved weight loss in overweight individuals in combination with a hypocaloric diet throughout the study.²⁴⁰ This suggests that probiotics might function to increase the efficacy of more conventional lifestyle interventions aiming to improve obesity and metabolic disorders.¹⁸³ Further, it is also suggested that their beneficial effects may not be primarily mediated through a reduction of food intake but rather changes of metabolism and increased energy expenditure.²⁴¹ To our knowledge, however, only Shirouchi et al.²⁴² have previously demonstrated that *Lactobacillus gasseri* SBT2055 fermented milk (6×10^7 CFU/g diet, 4 weeks) increased energy expenditure in a high fat-high sugar-induced obesity rat model.²⁴² Future studies should further explore how probiotic administration and microbiota changes through dietary approaches modifies both food intake and energy expenditure especially in humans.²⁴³ Given the complex nature of human studies and the promising findings regarding Oxt-based therapies, we suggest that combining probiotics with Oxt could provide an additional benefit in weight management, through better modulation of central appetite, reward and stress.

We hypothesize that Oxt is a major player involved in the modulation of food intake, and that the microbiome can also impact eating via Oxt. The current evidence linking both the microbiota and Oxt independently to food intake behavior, food reward and stress, warrants further investigation into the mechanisms and neurocircuitry involved in mediating their convergent effects.

5 | CONCLUSIONS

The Oxt neuropeptide has biological and behavioral functions that extend beyond parturition, lactation, and social behavior. More recently, it has been shown to also modulate eating behavior. Indeed, Oxt coordinates and integrates homeostatic signals derived mainly from the hypothalamus, but also the brainstem, with non-homeostatic signals from the mesocorticolimbic system and the hippocampus. Thereby, it controls not only energy and glucose metabolism, but also food intake through affecting brain centers involved in decision-making processes. At the same time, growing evidence suggests that this regulation of both homeostatic and non-homeostatic eating behaviors is interconnected with the gut microbiota. This adds the microbiota-gut-brain-axis as a player in the oxytocinergic regulation of brain function and behavior. Recent studies have shown that Oxt and the gut microbiota are tightly interlinked with potential significant outcomes on stress and social behaviors. However, a gap in knowledge at this point is whether these two key players also converge their influence on eating behavior. For this reason, further research is needed to elucidate the precise mechanisms underlying the effects of Oxt and the gut microbiota on homeostatic and non-homeostatic regulation of eating behavior, but also their combined impact. Furthermore, stress is an additional factor that modulates each of these players independently, but it remains unknown how gut microbiota-

and Oxt-mediated effects on eating behavior would be impacted by stress or in conditions of dysregulated eating. Future research in this area needs to step away from solely demonstrating a correlation between these puzzle pieces, but move towards understanding causality, the mechanisms of action and the involved neurocircuitry.

Understanding this knowledge gap should foster further studies to investigate microbiota interventions targeting the Oxt system as a potential treatment not only for neurodevelopmental disorders and social disorders but also in the context of stress-related disorders and eating disorders, in stress and non-stress contexts.

AUTHOR CONTRIBUTIONS

Cristina Cuesta-Marti: Conceptualization; investigation; methodology; writing – original draft. **Friederike Uhlig:** Supervision; writing – original draft; writing – review and editing. **Begoña Muguerza:** Supervision; validation; writing – review and editing. **Niall Hyland:** Writing – review and editing. **Gerard Clarke:** Resources; supervision; writing – review and editing. **Harriët Schellekens:** Conceptualization; resources; supervision; writing – review and editing.

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CONFLICT OF INTEREST

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Friederike Uhlig  <https://orcid.org/0000-0001-7441-1951>

Begoña Muguerza  <https://orcid.org/0000-0001-7384-8588>

Harriët Schellekens  <https://orcid.org/0000-0002-6065-3797>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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