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The inflammatory event of birth: How oxytocin signaling may guide the development of the brain and gastrointestinal system

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ABSTRACT

The role of oxytocin (OT) as a neuropeptide that modulates social behavior has been extensively studied and reviewed, but beyond these functions, OT's adaptive functions at birth are quite numerous, as OT coordinates many physiological processes in the mother and fetus to ensure a successful delivery. In this review we explore in detail the potential adaptive roles of oxytocin as an anti-inflammatory, protective molecule at birth for the developing fetal brain and gastrointestinal system based on evidence that birth is a potent inflammatory/immune event. We discuss data with relevance for a number of neurodevelopmental disorders, as well as the emerging role of the gut-brain axis for health and disease. Finally, we discuss the potential relevance of sex differences in OT signaling present at birth in the increased male vulnerability to neurodevelopmental disabilities.

1. Introduction

The role of oxytocin (OT) as a neuropeptide that modulates social behavior has been extensively studied and reviewed in recent years (Carter, 2017a,b; Carter et al., 1995, 2008; Young et al., 2011; Young and Wang, 2004). Beyond these functions, some of OT's most important functions are associated with the delivery process, including the stimulation of uterine contractions and milk letdown for lactation. Moreover, OT's adaptive functions at birth are quite numerous, as OT appears to coordinate many physiological processes in the mother and fetus to ensure a successful delivery, such as fetal analgesia, fetal lung maturation, expulsion of the placenta, and enhanced mother-infant bonding for first feeding. In this review we focus on the functions of OT at this critical time-point and explore in detail the potential adaptive roles of oxytocin as an anti-inflammatory, protective molecule at birth for the developing fetal brain and gastrointestinal system. For offspring, birth is an inflammatory/immune event characterized by hypoxic-like conditions during delivery (Lagercrantz and Slotkin, 1986; Maron et al., 2010; Tyzio et al., 2006), a surge in stress hormones (Lagercrantz and Slotkin, 1986), elevated fetal cytokines (Castillo-Ruiz et al., 2018a; Golightly et al., 2011), antigen stimulation through microbial colonization (Castillo-Ruiz et al., 2018a; Costello et al., 2012) and amino acid insufficiency stress (Klein et al., 2017). OT is a potent anti-inflammatory molecule (Li et al., 2016; Wang et al., 2015) that reduces gut inflammation in models of colitis (Cetinel et al., 2010; Welch et al., 2014) and cellular stress in gut epithelial cells (enterocytes) following bacterial endotoxin exposure (Klein et al., 2017, 2014). Thus, we explore the possible adaptive roles of OT for the developing gut, including the modulation of inflammatory processes during microbial colonization at birth (Klein et al., 2016) and amino acid insufficiency stress that occurs in enterocytes before the first feeding of colostrum (Klein et al., 2017). Within the brain, parturition is associated with a surge in brain pro-inflammatory cytokines and widespread modulation of neuronal cell death (Castillo-Ruiz et al., 2018b). Because OT has been shown to reduce brain inflammation in postnatal and adult animals by limiting oxidative stress and cytokine release from microglia (Amini-Khoei et al., 2017; Karelina et al., 2011; Yuan et al., 2016), OT may be similarly protective for the brain at birth during the hypoxic-like conditions of delivery and natural elevation of brain cytokine levels. Importantly, OT receptors (OTRs) are expressed in the fetal brain (Tyzio et al., 2006) and gut (Welch et al., 2009) during the perinatal period, suggesting important roles for OT signaling during this critical event.

We next consider what is known about the alteration of OT signaling at birth and the risk for various neurodevelopmental disorders. As part of this discussion, we describe the emerging role of the gut-brain axis since alterations in this axis have the potential to shift developmental trajectories and influence disease processes. The gut-brain axis refers to the bidirectional signaling that occurs between the gastrointestinal tract

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and the nervous system and is characterized by neural, hormonal, biochemical and immunological routes of communication (Cryan and Dinan, 2012). If we consider the microbial organisms within the gut, it is referred to as the microbiome-gut-brain-axis and accounts for the role that these microorganisms play in this bidirectional signaling. It is becoming increasingly recognized that disturbances of the gut microbial ecosystem can create intestinal dysfunction and inflammation that gives rise to abnormal social behavior and cognition (Cryan and Dinan, 2012). One mechanism by which the brain and gut communicate with each other is via the vagus nerve and we discuss recent studies that demonstrate that OT is an integral player within this signaling pathway that gives rise to normal social behavior (Buffington et al., 2016; Sgritta et al., 2019).

Finally, we discuss how sex differences present at birth may make males particularly vulnerable to the hypoxic-like conditions of delivery, particularly if the hypoxia is prolonged or elevated due to adverse events of labor. Compared to males, females may be more resilient based on their hormonal milieu at birth and an inherently greater antioxidant capacity within their brains.

2. Introduction to OT and its receptors

The neuroendocrine hormone OT is a highly conserved nine amino acid peptide ("nonapeptide") that arose through a duplication event of the ancestral gene, arginine vasotocin, more than 600 million years ago (Acher and Chauvet, 1995). The present day canonical form of OT (Leu^8-OT) dates back to eutherian mammals and was first well described by Du Vigneaud (Du Vigneaud et al., 1953) and Archer (Acher and Fromageot, 1955). OT is primarily produced by magnocellular and parvocellular neurons within the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus (Brownstein et al., 1980; Young and Gainer, 2003). Magnocellular neurons within these nuclei project to the posterior pituitary gland and release OT directly into the bloodstream where it can act as a hormone and bind to oxytocin receptors (OTRs) in the periphery to regulate smooth muscle function (Carter et al., 2008; Neumann, 2009), such as the stimulation of uterine contractions during parturition and milk letdown during lactation (Belin et al., 1984; Fuchs and Poblete, 1970). Magnocellular neurons also release OT directly into the brain via dendritic release (Ludwig and Leng, 2006), as well as via axon collaterals, which project more distantly to brain regions such as the nucleus accumbens (Ross et al., 2009) and the central amygdala (Knobloch et al., 2012). In addition to magnocellular neurons, the PVN contains parvocellular neurons that project to the median eminence and release OT into the hypophyseal portal system, a network of blood vessels that carries hormones to the anterior pituitary and releases them into the systemic circulation. These parvocellular neurons are major modulators of the hypothalamic-pituitary-adrenal (HPA) axis, the body's central stress response system (Landgraf and Neumann, 2004). OT is a well-known suppressor of the HPA axis and reduces responses to both social and physical stressors (Neumann et al., 2000; Windle et al., 1997), facilitates anxiolysis and enhances stress coping (Kelly and Goodson, 2014; Smith and Wang, 2014). It is likely that OT's central and peripheral effects serve to coordinate natural physiological processes within the body with appropriate social behavior. For instance, the spike in plasma OT that is observed in conjunction with the expulsion of the placenta and intense uterine contractions postpartum within women coincides with a sensitive period characterized by enhanced mother-infant bonding and first feeding (Nissen et al., 1995).

Within mammals, OT signals through its G protein-coupled receptor, OTR, but can bind with lower affinity to the vasopressin receptors, V1aR, V1bR, and V2R (Ocampo Daza et al., 2012; Song and Albers, 2018). Because OT and the related nonapeptide, arginine vasopressin (AVP), as well as their receptors (OTR, V1aR, V1bR and V2R), are structurally similar, these peptide hormones display promiscuity for each other's receptors. Thus, endogenous and exogenous release of OT and AVP can result in receptor cross-talk depending on nonapeptide concentration, synaptic versus non-synaptic release of OT and AVP, and location and density of the OTRs, V1aRs, V1bRs and V2Rs within the brain and periphery (Song and Albers, 2018). Along these lines, it is important to consider that: (1) OT has higher affinity for OTRs than for V1aRs and V1bRs, while AVP has similar affinity for OTRs, V1aRs and V1bRs, (2) OT and AVP can have opposing roles on physiology and behavior, (3) receptors densities for OT and AVP have very little brain overlap, (4) there is currently very limited evidence of receptor cross-talk following endogenous OT or AVP release, and (5) cross-talk is more likely to occur during non-synaptic release and following the administration of high exogenous levels of OT or AVP (reviewed in Song and Albers, 2018). For example, a moderately high concentration of OT can act as an agonist at V1aRs in the periphery (Levasseur et al., 2004). With regards to inflammation, OT and AVP may also have opposing roles (Bordt et al., 2019; Carter, 2007) but again this is dependent on peptide concentration and receptor binding. Given these considerations and the fact that OT and AVP activate various downstream signaling pathways depending on which G proteins are coupled to their receptors, dose-response studies and the administration of selective agonists and antagonists are essential for understanding the ligand-receptor interactions and effects of these peptides. In the subsequent sections, we discuss the various roles for OT signaling during the birth process, including the use of agonists, antagonists and receptor KO mice that demonstrate the receptor-mediated specificity of OT's effects.

3. Well-known protective functions of OT at birth (outside of the brain and gastrointestinal system)

Perhaps two of the most well known functions of OT are the stimulation of uterine contractions during parturition and milk letdown during lactation. However, additional studies suggest that OT plays a significantly greater adaptive role at birth and serves to coordinate multiple physiological processes within the fetus to maximize physiological and behavioral outcomes. For instance, OT released during labor facilitates fetal lung maturation by contributing to epinephrine secretion. This elevation in plasma epinephrine levels following oxytocin-induced labor stimulates ß-adrenoreceptors, which induces $Na+$ transport across the alveolar membrane and causes the fetal lungs to absorb fetal lung fluid in preparation for respiration (Nair et al., 2005; Norlin and Folkesson, 2001). Furthermore, an increase in the production of lung surfactant is associated with the natural increase in catecholamines (i.e. norepinephrine and epinephrine) immediately prior to birth (Lagercrantz and Slotkin, 1986), as well as an oxytocin-induced labor, as apposed to a Cesarean birth without labor (Rooney et al., 1977). Lung surfactant decreases surface tension in lung alveoli, allowing them to remain open, facilitating respiration (Lagercrantz and Slotkin, 1986). Besides lung maturation, the surge in catecholamines arising from the adrenal gland before birth has several other adaptive functions during parturition, such as shunting blood flow to vital organs and reducing fetal heart rate, both of which protect the fetus during the intermittent oxygen deprivation associated with contractions of the uterus (Lagercrantz and Slotkin, 1986). This surge in catecholamines also breaks down energy stores to produce glucose, free fatty acids and glycerol in preparation for the temporary cessation of nutrients (Lagercrantz and Slotkin, 1986). The release of catecholamines from the adrenal medulla is likely due to the stress/hypoxia-like conditions of birth and the pressure on the fetal head during uterine contractions. Because OT-induced labor has been shown to increase epinephrine secretion (Nair et al., 2005; Norlin and Folkesson, 2001), OT likely augments these catecholamine-mediated physiological responses.

OT also serves as an analgesic for the fetus precisely at the time of delivery. Mazzuca examined whether analgesia in newborn rats is mediated by OT release during labor (Mazzuca et al., 2011) based on (1) the observation that infants born via a spontaneous vaginal birth have dampened behavioral and physiological responses to painful stimuli in the 90 min after birth compared to infants born via planned

elective Cesarean-section (C-section) (Bergqvist et al., 2009) and (2) that cord blood of vaginally born infants has higher levels of OT than infants delivered via planned C-section (Marchini et al., 1988). Compared to postnatal day 2 (PND 2) rats, newborn rats born via a spontaneous vaginal delivery and tested within 2 h of birth display an increased latency of tail withdrawal to painful stimuli. A delay of tail withdrawal could be increased with an OT intraperitoneal (IP) injection at birth and rapidly accelerated with an OTR antagonist IP injection, demonstrating that the analgesia is mediated by OT signaling. Based on the similar effects of OT and bumetanide, a blocker of the Na^+-K^+-$2Cl^-$ (NKCC1) co-transporter, OT likely promotes analgesia by inhibiting the NKCC1-mediated accumulation of intracellular chloride ($[Cl^-]_i$) within nociceptive neurons. A fall in $[Cl^-]_i$ reduces the driving force of γ-aminobuyturic acid (GABA) and increases GABAergic inhibition on trigeminal sensory neurons, alleviating pain (Mazzuca et al., 2011). Interestingly, this mechanism by which OT mediates fetal analgesia at birth is (1) TRPV1 receptor independent (Mazzuca et al., 2011), in contrast to OT's effects on neuropathic pain in adults (Sun et al., 2018), and (2) the same mechanism by which OT protects the fetal brain from hypoxia during delivery (discussed in detail below; Tyzio et al., 2006).

To summarize, OT's adaptive functions at birth include the stimulation of maternal uterine contractions and milk letdown, fetal lung maturation and analgesia, and enhanced epinephrine production in the fetus that may contribute to glucose production, reduced heart rate and the redirecting of blood flow to vital organs. Given that OTRs are expressed in the perinatal brain (Tyzio et al., 2006; Sannino et al., 2017), we now move on to discuss the roles of OT at birth for the developing nervous system.

4. OT's potential neuroprotective effects for the brain at birth

OT's remarkable adaptive and neuroprotective effects for the fetal brain at birth were demonstrated by Tyzio et al. (2006), in which OT was shown to protect neurons from the hypoxic-like conditions of delivery by switching the action of GABA signaling. In addition to providing neuroprotection at birth via a GABA switch, additional adaptive functions of OT may include microglia inhibition and a reduction in oxidative stress. For instance, within postnatal and adult models of hypoxia-ischemia, an early life stress model and bacterial endotoxin exposure, OT has been shown to inhibit microglia-mediated inflammatory cascades and protect mitochondrial function by limiting oxidative stress. Furthermore, based on OT's well-described modulation of cellular stress and protein synthesis within gut enterocytes, including newborn enterocytes, we speculate that OT may also modulate cellular stress within neurons at birth.

4.1. The GABA switch at birth protects against hypoxia

During labor, a fetus is subjected to hypoxic-like conditions that are created by contractions of the uterus, which result in intermittent oxygen supply due to the compression of the umbilical cord and placenta, as well as compression of the head as it passes through the birth canal (Lagercrantz and Slotkin, 1986). Interestingly, OT protects the fetal brain from hypoxia at birth by mediating an excitatory to inhibitory switch in GABA signaling within neurons (Tyzio et al., 2006), a mechanism that is virtually identical to that conferred by OT to the fetus against nociceptive pain during delivery (Mazzuca et al., 2011). Whereas GABA is depolarizing during both fetal and early postnatal periods in rats and serves to drive neural activity in immature cells (McCarthy et al., 2002), GABA transiently switches to hyperpolarizing in the 2 days surrounding birth (Tyzio et al., 2006; Khazipov et al., 2008). Tyzio et al. (2006) have beautifully demonstrated that (1) maternal OT is both necessary and sufficient for the excitatory to inhibitory switch in GABA signaling in fetal brain tissue at birth that provides protection against hypoxia, and (2) OT mediates this switch through a reduction in $[Cl^-]_i$, likely by down-regulating the chloride inward cotransporter 1 (NKCC1). Furthermore, in a model of anoxia-aglycemia that simulates birth conditions, maternal OTR antagonism accelerates fetal hypoxic brain injury while administration of the NKCC1 antagonist bumetanide delays it, supporting the hypothesis that OT-mediated hyperpolarization of fetal neurons precisely at birth serves to greatly reduce their metabolic demand and concomitantly increase their resistance to anoxia during the delivery process (Tyzio et al., 2006; Khazipov et al., 2008).

Interestingly, in two distinct rodent models of autism (valproate and fragile X), the excitatory to inhibitory switch in GABA signaling that coincides with birth is absent, fetal neurons are characterized by abnormal excitatory GABA and increased glutamatergic activity, and fetuses display aberrant brain oscillations and abnormal ultrasonic vocalizations (Tyzio et al., 2014). The valproate model is based on studies showing an increased risk of autism in children exposed to the anti-epileptic drug, valproic acid, during pregnancy (Christensen et al., 2013; Nicolini and Fahnestock, 2018). Mothers are typically administered valproate during pregnancy for epilepsy, migraine headaches and mania associated with bipolar disorder. The increased autism risk is found in offspring independent of maternal epilepsy diagnosis, suggesting a biological association between valproate and autism (Nicolini and Fahnestock, 2018). While the mechanism by which valproic acid increases autism risk is unclear, valproate has been shown to increase GABA levels through its inhibition of enzymes that degrade GABA (e.g. GABA transaminases) and through stimulation of glutamic acid decarboxylase, an enzyme that increases GABA production (Loscher, 2002). Thus, valproate given prenatally could increase the excitatory nature of GABA early in development. Fragile X syndrome is an inherited intellectual disability caused by the hyper-methylation of the fragile X mental retardation 1 (FMR1) gene during the first trimester in humans that leads to the eventual silencing of the gene and the absence of FMR1 protein. Within this model, alterations in glutamate-dependent and GABA-dependent signaling, as well as enhanced neuronal excitability, have been reported (Telias, 2019).

Importantly, in both valproate-exposed rats and mice carrying the fragile X mutation (FRX mice), application of OT or bumetanide to brain cultures, or maternal pre-administration of bumetanide before birth, restores the excitatory to inhibitory developmental sequence in GABAergic signaling, reinstates physiological brain oscillations, and normalizes offspring vocalizations (Tyzio et al., 2014). Conversely, maternal administration of an OTR antagonist just before birth prevents the switch in GABA signaling, exacerbates glutamatergic activity, and produces altered vocalizations and abnormal nest-seeking behavior in offspring (Tyzio et al., 2006; Tyzio et al., 2014). Furthermore, the increased spontaneous activity and enhanced gamma oscillations that characterize brain tissue from valproate-treated rats, but not control or bumetanide-treated rats, can be observed at PND 15, indicating that failure to induce the excitatory to inhibitory GABA switch at birth has lasting consequences for brain activity, as well as for emergent social behavior (Tyzio et al., 2014). Within humans, children whose mothers were administered the OTR antagonist Tractocile near birth for pre-term labor had worse scores on the Autism Diagnostics Observation Schedule (ADOS), as compared to children born to mothers that (1) did not receive OTR antagonism but did receive another pre-term labor drug (Nifedipine) or (2) no drugs at all (Friedlander et al., 2017). Specifically, the prevalence of ASD within the OTR antagonism group was 10.7%, as compared to 2.7% in the no treatment group and 1–4% in the general population.

In addition to the critical window for OT action at birth, it appears that there is another critical postnatal window of OT action for GABAergic signaling. Of note is that the normal developmental sequence of GABAergic activity is biphasic: GABAergic signaling is depolarizing before birth, hyperpolarizing precisely at birth (first switch in GABA polarity), excitatory again shortly after birth and then inhibitory (second GABA switch) after the first postnatal week into

adulthood (McCarthy et al., 2002; Tyzio et al., 2014). When the OT-mediated switch in GABA signaling does not occur at birth, as in valproate and fragile X rodent models of autism, the entire sequence of GABA signaling is significantly altered such that the driving force of GABA remains excitatory throughout this developmental sequence (Tyzio et al., 2014). Thus, the absence of a switch in GABAergic signaling at birth likely has significant consequences for the development of proper excitatory/inhibitory (E/I) balance within neural circuits, which mediates normal social and behavioral functions (Bartos et al., 2007; Fuchs et al., 2007; Sohal et al., 2009). Interestingly, OT also directs the excitatory to inhibitory switch in GABAergic signaling that occurs postnatally (Leonzino et al., 2016). Specifically, (Leonzino et al., 2016) demonstrated that OT signals through an OTR/Gq/Protein Kinase C (PCK) dependent pathway to upregulate and stabilize the K^+-Cl^- outward cotransporter 2 (KCC2) in the plasma membrane of neurons (Leonzino et al., 2016). KCC2 functions to lower $[Cl^-]_i$, mediating the permanent switch to hyperpolarization. In OTR knockout (KO) mice, the upregulation of KCC2 is impaired, the GABA switch is delayed and the mice are characterized by an excitatory/inhibitory (E/I) imbalance with increased excitation and susceptibility to seizures (Leonzino et al., 2016; Sala et al., 2011), as well as autistic-like behaviors (Sala et al., 2011). Thus, OT signaling is required at birth, as well as within the early postnatal period, to mediate two switches in GABAergic signaling that are essential for the establishment of proper E/I balance within cortical circuits. Interestingly, the OTR can have opposing effects on neuronal excitability through its promiscuous coupling to Gq and Gi proteins that differentially regulate potassium currents involved in olfactory E/I balance (Gravati et al., 2010).

To summarize, the OT-mediated GABA switch at birth not only establishes proper E/I balance within postnatal cortical circuits but also greatly reduces the metabolic demand of neurons by decreasing $[Cl^-]_i$ (Tyzio et al., 2006; Khazipov et al., 2008). Because maintaining elevated $[Cl^-]_i$ within neurons requires substantial energy, the OT-mediated GABA switch effectively reduces the energetic demands of cells, increasing their resistance to the hypoxic-like conditions at birth when ATP levels are limited (Tyzio et al., 2006; Khazipov et al., 2008; Ceanga et al., 2010). Since animals models of hypoxia/ischemia outside of birth are characterized by increases in pro-inflammatory microglial signaling, oxidative stress and reactive oxygen species (Butturini et al., 2019; Tang et al., 2019), we speculate that additional adaptive functions of OT at birth include the dampening of microglial activation and oxidative stress in the fetal brain during the acute phase of delivery.

4.2. Inhibition of inflammatory cascades and cytokine release from microglia

Within postnatal and adult animals, OT is a potent anti-inflammatory molecule (Li et al., 2016; Wang et al., 2015) that reduces brain inflammation by limiting oxidative stress and pro-inflammatory cascades mediated by microglia (Amini-Khoei et al., 2017; Karelina et al., 2011; Yuan et al., 2016). In a model of ischemic stroke, experimental animals socially housed (which releases endogenous hypothalamic OT) after focal cerebral ischemia have reduced infarct size, increased antioxidant activity via an elevation of glutathione peroxidase (GPx) and decreased oxidative stress via an elevation in the ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG), relative to animals placed in social isolation (Karelina et al., 2011). Pretreatment with an OTR antagonist blocks these effects in socially housed mice while pretreatment with exogenous OT induces the protective effects in socially isolated mice. Karelina et al. (2011) suggest that OT provides this neuroprotection through the suppression of microglial reactivity as (1) microglia have been shown to exacerbate ischemic damage (Yrjanheikki et al., 1999) and (2) OT reduces lipopolysaccharide (LPS)-induced expression of MHC Class II (a marker of microglial activity) within cultured microglia prepared from the socially isolated mice (Karelina et al., 2011).

Additional studies have reported that the anti-inflammatory action of OT is mediated through the OTR, which is upregulated in response to inflammatory stimuli and acts as an acute phase protein to suppress macrophage/microglia-mediated inflammatory cascades. For instance, LPS stimulation of primary human macrophages up-regulates OTR transcription and OTR protein expression via NF-κB, as well as interleukin-6 (IL-6), and co-incubation with OT reduces IL-6 secretion from the LPS-stimulated macrophages (Szeto et al., 2017). Similarly, LPS-stimulation of primary murine microglia also increases OTR expression and protein, as well as the production of the pro-inflammatory mediators TNFα, IL-1β, COX-2 and iNOS, the latter of which are all significantly decreased if LPS-stimulated cultures are pretreated with OT (Yuan et al., 2016). Additionally, OT suppresses acute inflammation following an IP injection of LPS within an *in vivo* model. Specifically, intranasal administration of OT to adult male mice one hour prior to an IP LPS injection reduces levels of TNFα, IL-1β, COX-2 and iNOS, as well as Iba1+ (microglial marker) cells in the prefrontal cortex of mice measured at 4 h (mRNA expression) and 24 h (protein expression) later, as compared to mice that received only the LPS injection (Yuan et al., 2016).

Most recently, OT signaling via OTR has been shown to be protective for the developing rat brain by inhibiting microglial activation during the *perinatal* period in the context of a double-hit model of inflammatory brain injury (Mairesse et al., 2019). In this model, offspring are exposed to a low protein diet (LPD) throughout gestation (1st hit) followed by postnatal injections of IL-1β on PND 1 and PND 2 (2nd hit). Co-administration of the OTR *agonist* carbetocin with IL-1β at PND 1 and PND 2 produced a ~50% reduction in the genes up-regulated more than 1.5-fold in microglia isolated from rats in the LPD/IL-1β double-hit experimental condition, compared to microglia from non-carbetocin-treated offspring. The genes decreased by carbetocin treatment include classical pro-inflammatory markers released by cytotoxic microglial activation such as IL-1β, IL-6, TNFα and iNOS (Mairesse et al., 2019). Furthermore, within the TNFα-NFκB pathway, 57 genes that were up-regulated 1.41 fold in microglia from LPD/IL-1β treated animals were down-regulated 0.81-fold by carbetocin administration. In primary microglial cultures from LPD animals, carbetocin treatment also reduced the IL-1β + INFγ-mediated increase in IL-6, TNFα and iNOS expression, an effect that was blocked by co-incubation with an OTR antagonist. Further *in vivo* analyses within the double-hit model demonstrated that carbetocin protects myelination, intrahemispheric connectivity and the development of normal anxiety-like behavior. Remarkably, in a hydrocortisone-induced model of neuroinflammation within zebrafish, carbetocin promoted the recovery of activated microglia cells to a ramified morphology and down-regulated the hydrocortisone-induced elevation of IL-1β and TNFα, demonstrating that the neuroprotective function of oxytocin signaling near birth is highly conserved across species (Mairesse et al., 2019). Altogether these studies demonstrate that, in the presence of significant inflammatory stimuli, OT signaling provides neuroprotection by dampening pro-inflammatory cascades mediated by microglia (Karelina et al., 2011; Yuan et al., 2016; Mairesse et al., 2019). Interestingly, within these models, OT signaling does not appear to confer neuroprotection in the absence of these inflammatory stimuli (Yuan et al., 2016; Mairesse et al., 2019), suggesting that reductions of OT at birth (i.e. a major stressor characterized by inflammatory signaling) is likely to have greater neural consequences, as compared to OT manipulations outside of the birth period.

4.3. Effects on oxidative stress and mitochondria

OT is also able to reduce brain inflammatory process by limiting oxidative stress associated with mitochondrial dysfunction. Within an animal model of depression induced by early maternal separation stress (MS), Amini-Khoei et al. (2017) examined whether OT administration in adult males could prevent depressive-like symptoms by acting as an

antioxidant and anti-inflammatory molecule in animals subjected to postnatal separation stress. Adult male offspring exposed to MS from PND 2-PND 14 for 3 h a day showed decreased mobility during a forced swim task, decreased grooming activity during a sucrose splash test and decreased sucrose intake in a sucrose preference test. Within hippocampal mitochondria, MS decreased levels of GSH and ATP and increased levels of nitrite and reactive oxygen species (ROS). An examination of immune-inflammatory markers from hippocampal tissue showed that MS significantly increased the expression of TNFα, IL-1β, MyD88, toll-like 4 receptor (TLR4) and Nlrp3. Remarkably, intraventricular injections of OT (1 μg) in adult males prior to behavioral tests attenuated depressive-like behaviors, restored mitochondrial dysfunction, and decreased the expression of genes that mediate immune-inflammatory responses. Furthermore, all of OT's protective effects for the brain and behavior were blocked if the OTR antagonist Atosiban was administered alone or together with OT. Thus, OT has anti-depressant properties through its ability to restore mitochondrial function and neuroinflammation in adult animals that experienced an early life stressor (Amini-Khoei et al., 2017).

There is also recent evidence that OT can reduce oxidative stress and preserve mitochondrial function in the context of hypoxia-ischemia (Kaneko et al., 2016), which suggests that OT may protect mitochondrial function during the hypoxic-like conditions of birth (Lagercrantz and Slotkin, 1986; Khazipov et al., 2008). During oxygen-glucose deprivation (OGD), an *in vitro* paradigm often use to model hypoxia-ischemia at birth (Tyzio et al., 2006; Ceanga et al., 2010), neurons first enter adaptation, a phase in which cells decrease neuronal activity and use intracellular energy stores to maintain ionic gradients and membrane potential. This phase is reversible if oxygen is restored but if the hypoxia continues, neurons progress to anoxic depolarization (AD), a state that is characterized by significant cell death due to (1) the exhaustion of intracellular energy stores, (2) a crash in ATP levels and ATP-dependent ionic transports, (3) a rise in intracellular Ca^{2+} and (4) a subsequent increase in ROS (Khazipov et al., 2008). At birth, OT slows the neuronal progression to AD during both OGD (Tyzio et al., 2006) and the re-oxygenation stage (Tyzio et al., 2006) by inhibiting the elevation of intracellular $[Cl^-]_i$, which preserves energy by reducing metabolic demand (Tyzio et al., 2006; Khazipov et al., 2008). Conversely, OTR antagonism accelerates the time to AD during both OGD and OGD-reoxygenation (Tyzio et al., 2006; Ceanga et al., 2010). Interestingly, OT has dose-dependent effects on this process *in vitro* that are characterized by an inverted U-shaped curve (Ceanga et al., 2010), which may have implications for the modulation of OT concentration at birth. Specifically, a 1 μM concentration of OT was maximally neuroprotective for fetal neurons at birth while cell viability was greatly reduced at lower or higher concentrations of OT (Ceanga et al., 2010). With regards to mitochondrial function, rat primary neural cells exposed to OGD display decreased mitochondrial activity, (as measured by the MTT assay) and decreased cell viability, in addition to increased GSSG activity and increased extracellular levels of high motility group Box 1 (HMGB1), which elevates ROS (Kaneko et al., 2016). HMGB1 is a chromatin protein released by necrotic and inflammatory cells that can activate microglia through the receptor for advanced glycation end products (RAGE) (Massey et al., 2019). Thus, primary neural cell cultures subjected to OGD conditions that model hypoxia-ischemia at birth are characterized by increased oxidative stress, decreased mitochondrial function and perhaps increased microglia activation via HMGB1 (Kaneko et al., 2016). Furthermore, primary neural cells (from E18 rat cortex) pretreated with OT before OGD exposure displayed increased mitochondrial activity, decreased GSSG activity, decreased HMGB1 levels and increased cell viability, effects consistent with an anti-inflammatory and neuroprotective function of OT during hypoxic-ischemic events. All of these OT-mediated neuroprotective effects were blocked in the presence of Atosiban, an OTR antagonist, demonstrating that the protection is likely through OT-OTR signal transduction (Kaneko et al., 2016). Consistent with these findings, the serum and plasma of pregnant women administered Atosiban for 48 h to block pre-term labor were characterized by increased oxidative stress and reduced antioxidant capacity (measured as an increase in total oxidative status, oxidative stress index, and carbonyl groups, as well as a decrease in total antioxidant status), as compared to the serum of women that did not receive Atosiban treatment for pre-term labor (Grzesiak et al., 2018). Similarly, injections of Atosiban to pregnant rats during the last five days of pregnancy resulted in elevated oxidative stress in the plasma of newborn rats delivered at term, as compared to that of term offspring whose mothers were injected with saline (Simsek et al., 2012).

In summary, OT confers neural protection by preserving mitochondrial function and reducing oxidative stress in adults subjected to early life separation stress and in primary neural cultures modeling hypoxia/ischemia at birth. To follow up on these findings, it would be important to assess mitochondrial function, oxidative stress levels and cell viability *in vivo* after manipulations of OT levels at birth. In the next section, we examine OT's potential protective role in modulating cellular stress via the unfolded protein response. This inquiry is based on OT's known roles in the modulation of the unfolding protein response, inflammatory cascades and oxidative stress within gastrointestinal tissue (described in detail in sections below).

4.4. Unfolded protein response and potential Autism link

While speculative, OT may provide neuroprotection near birth by modulating the unfolded protein response in the endoplasmic reticulum (UPR^{ER}) of cells, a protective mechanism during cellular protein synthesis (Bordt et al., 2019; Klein et al., 2014). Within the endoplasmic reticulum (ER), proteins undergo proper folding and post-translational modifications during translation (Schroder and Kaufman, 2005a). An increase in cellular stress during this process can lead to a buildup of unfolded or misfolded proteins within the ER, causing ER stress. Cells will then activate a stress response, called the UPR^{ER}, that functions to restore cellular homeostasis by engaging signaling systems that both halt protein translation and reduce the unfolded/misfolded protein load (Hetz, 2012; Hetz et al., 2011; Schroder and Kaufman, 2005b). Not surprisingly, the UPR^{ER} is important for the regulation of metabolic, stress and immune pathways (Bordt et al., 2019). Interestingly, OT can regulate various effector molecules of the UPR^{ER} in an attempt to reduce cellular stress (Klein et al., 2013, 2014, 2016, 2017). Furthermore, in enterocytes *in vitro*, OT has been shown to specifically modulate the PI3K/Akt/mTORC1 pathway involved in protein translation (Klein et al., 2014, 2013). Both low and high concentrations of OT were shown to phosphorylate Raptor, thereby blocking mTORC1 signaling. As further evidence of mTORC1 inhibition, OT treatment decreased the phosphorylation of $4E\text{-}BP1^{S65}$ (a mTORC1 substrate), which serves to keep eIF4E bound to $4E\text{-}BP1^{S65}$, thereby halting protein synthesis (Klein et al., 2013). Thus, the endogenous release of OT at birth may inhibit mTORC1 signaling in neurons in order to halt protein translation under conditions of increased cellular stress (i.e. birth), thereby serving as a protective mechanism against ER stress (Klein et al., 2014, 2013). With regards to the developing brain and autism, Kelleher and Bear have suggested that a loss of constraints on synaptic activity-induced protein synthesis may underlie some aspects of autism pathologies (Kelleher and Bear, 2008). For instance, PTEN phosphatase inhibits the PI3K/mTORC1 pathway (like OT), thereby blocking protein synthesis, and loss of function mutations in PTEN is linked to autism spectrum disorder (ASD). Furthermore, other gene products that normally inhibit protein translation are mutated in single-gene disorders linked to ASD, such as Fragile X syndrome (15–30% of affected individuals have ASD) and Tuberous sclerosis complex (25–60% of affected individuals have ASD) (Kelleher and Bear, 2008). Thus, defects in the activation of the UPR^{ER} and repression of protein synthesis may contribute to ASD phenotypes (Kelleher and Bear, 2008), and OT, as a regulator of the UPR^{ER} and protein synthesis, may be adaptive for the fetal brain at delivery in instances of heightened cellular stress. In support of this

Box 1
A comparison of human and rodent brain development.

Human gestation is 270 days while gestation in mice and rats is 18.5 days and 21 days, respectively. One consequence of these gestational differences is that the human brain is more advanced at birth in terms of its overall growth, as compared to rodents. For instance, the amount of cerebral cortical growth that has occurred in humans at birth (i.e. 270 days) occurs after birth in mice at PND 29 and at PND 31 in rats (Workman et al., 2013). Along these lines, the peak of dendritic growth and spinogenesis, as well as the period of giant depolarizing potentials that characterizes immature brain activity, occur *in utero* in macaques but largely in the postnatal period in rats (Ben-Ari, 2014). With regards to the OT system, hypothalamic OT neurons are generated in the midpoint of human pregnancy and in the second half of gestation in mice and rats (Sannino et al., 2017), although functional OT peptide in the fetus is not present until after birth (Sannino et al., 2017), suggesting that the effects described here for OT at birth are due to maternal OT acting on fetal OTRs that are already present at birth in rodents and humans (Marchini et al., 1988; Tyzio et al., 2006). Interestingly, the overall excitation to inhibition shift in GABA signaling during development has been observed across vertebrates, indicating this it is a heavily conserved feature across evolution (Ben-Ari, 2014). In terms of the excitatory to inhibitory shift in GABA signaling that coincides with birth, it has been well described in rats and mice but has not yet been examined in humans due to the difficulties in measuring such a shift in human infants on the day of birth (Ben-Ari, 2014). However, within rodents, the GABA shift that occurs at birth in hippocampal neurons also occurs in nociceptive neurons via an identical mechanism (i.e. a reduction in $[Cl^-]_i$) that serves to elevate pain thresholds and provide fetal analgesia. Intriguingly, human infants born via a spontaneous vaginal birth are characterized by increased pain thresholds (Mazzuca et al., 2011) and increased cord blood OT (Marchini et al., 1988), as compared to infants delivered by unlabored elective C-sections, suggesting that a similar protective GABA shift may occur in human neurons at birth. Furthermore, the concurrent development of parvalbumin GABAergic neurons (that mediate inhibition within cortical circuitry) and activity-dependent refinement of cortical circuits occur during a similar postnatal window in rodents and humans. Specifically, these processes begin after eye opening (postnatal day PND 10 in rats and PND 10–12 in humans) and occur during a critical period of sensory stimulation (postnatal weeks 3–4 in rodents and postnatal months 4–5 in humans) (Workman et al., 2013).

idea, Talos et al. demonstrated that hypoxia-induced neonatal seizures in rats enhance mTORC1 signaling, leading to long-term neuronal excitability, spontaneous seizures and autistic-like behavior (Talos et al., 2012).

In the following sections, we explore the roles of OT for the developing gastrointestinal system. Similar to the expression of OTRs in the brain, OTRs are present in various gut cells and tissues shortly before birth (Welch et al., 2009) and OTR knock out (KO) mice are characterized by a whole host of gut abnormalities (Welch et al., 2014), suggesting important roles for OT signaling within gastrointestinal tissue at birth.

5. OT's potential protective effects for the gastrointestinal system at birth and beyond

Parturition involves changes in inflammatory signaling since the fetal gastrointestinal tract must adapt to significant antigen stimulation via the introduction of thousands of species of bacteria at birth. Because OT (1) is a potent anti-inflammatory molecule for the gastrointestinal system (Cetinel et al., 2010; Welch et al., 2014; Iseri et al., 2008), (2) has several adaptive functions at birth and (3) is involved in signaling within the microbiome-gut-brain axis (Buffington et al., 2016; Sgritta et al., 2019; Varian et al., 2017), we hypothesized that OT is protective for the fetal gut during the birth process. This hypothesis is based on a disruption of gut architecture, increased permeability and increased inflammatory processes within the intestinal tissue of OTR KO mice (Welch et al., 2014), the presence of OTRs in various cell types within gastrointestinal tissue at birth (Welch et al., 2009) and OT's ability to reduce both gut inflammation in models of colitis (Cetinel et al., 2010; Welch et al., 2014) and cellular stress in cultured enterocytes (Klein et al., 2017, 2014).

5.1. Anti-inflammatory effects in adult colitis models

Consistent with OT's general role as an anti-inflammatory molecule (Li et al., 2016; Wang et al., 2015), OT is protective for the gastrointestinal system in the context of experimental models of colitis and gastric injury. In humans, ulcerative colitis is an immune-related chronic inflammatory bowel disease that is characterized by swelling, inflammation and the development of ulcers within the lining of the colon. Stress can further exacerbate the intensity of intestinal inflammation within this disease (Gulpinar et al., 2004; Lerebours et al., 2007). To examine OT's protective role in stress-aggravated colitis, adult rats were exposed to forced water stress, followed by the intracolonic administration of 2,4,6-trinitrobenzene sulfonic acid (TNBS) to induce colitis (Cetinel et al., 2010). A subset of rats received IP injections of OT or OT plus the OTR antagonist Atosiban for 3 days after colitis induction. Stress-aggravated colitis increased anxiety-like behavior and decreased exploratory behavior, increased gross macroscopic colonic damage and levels of malondialdehyde (MDA; a measure of lipid peroxidation), increased myeloperoxidase (MPO; a measure of neutrophil infiltration), and decreased levels of the antioxidant GSH. OT treatment significantly reduced all measures of colonic oxidative injury and alleviated anxiety, while OTR antagonism blocked OT's protective effects. Similar findings were observed following TNBS induced colitis in (1) OTR KO versus wild-type (WT) mice and (2) in WT mice given either OT or saline (Welch et al., 2014). Inflammation induced by experimental colitis in OTR KO mice was significantly greater than in WT littermates, as measured by clinical scores, histological score, and increased expression of inflammatory pathway genes. Conversely, within WT animals, exogenous OT treatment ameliorates the inflammatory damage of TNBS-induced colitis (Welch et al., 2014). Furthermore, in a model of burn-induced gastric injury in which gastrointestinal tissues are damaged from reduced intestinal blood flow, subcutaneous administration of OT reduces gastric damage scores and reverses burn-induced elevations of MDA and MPO within gastric tissue (Iseri et al., 2008). Thus, given the adaptive shunting of blood flow to vital organs during birth, such as the brain, heart, adrenal gland and placenta (and away from non-vital organs) (Lagercrantz and Slotkin, 1986), OT signaling may be particularly important for dampening these pro-inflammatory processes within gastrointestinal tissue during delivery. Furthermore, an absence of OT at birth or potential dose-dependent effects of OT (i.e. through the modulation of OT concentration at birth) could have significant unknown consequences for the gastrointestinal systems of infants at a time of reduced blood flow.

Both the increased susceptibility of OTR KO animals to gut inflammation and OT's improvement of inflammation in adult WT animals is consistent with the mature widespread expression of OTRs throughout the gastrointestinal tract (Welch et al., 2009). OTR transcripts are found in whole mouse gut, isolated samples from rat gut and in rat nodose ganglion. The nodose ganglion is an inferior ganglion of the vagus nerve and OTR immunoreactivity (-ir) is also observed in the nodose ganglion, demonstrating that vagal sensory neurons innervating the bowel express OTR. Within the adult myenteric plexus, ~70% of

enteric neurons are OTR-ir, and a subset of these OTR-ir neurons also have NeuN-positive cytoplasmic and nuclear staining, a marker of intrinsic primary afferent neurons (IPANs) (Van Nassauw et al., 2005). IPANs are peripheral neurons important for transducing physiological stimuli, such as villi movement, intestinal muscle contractions and chemical changes in gut contents, into neural activity within the enteric nervous system (ENS) (Furness et al., 2004). Importantly, IPAN excitability and signal transduction can be altered during inflammatory processes in the gut, with modifications persisting after the inflammatory state has passed (Clerc and Furness, 2004). Subsets of neurons are also OTR-ir in the submucosal plexus. Within the mucosal epithelium, crypt cells located at the crypt-villus junctions are OTR-ir. Because intestinal crypts generate precursor cells that mature into villus absorptive cells, OT-signaling at these crypt-villus junctions may regulate epithelial cell maturation (Welch et al., 2009). Alternatively, OT action through OTRs may regulate crypt cell secretion (Welch et al., 2009). Further examination of the apical OTR-ir in crypt epithelial cells using electron microscopy demonstrated that OTRs are present at the adherens junctions in enterocytes and appear to associate with sites of actin filament insertion into zonulae adherens (Welch et al., 2009). The function of adherens junctions, which lie basal to tight junctions in the epithelial wall, is to stabilize cell-cell contacts between enterocytes and maintain the physical integrity of the epithelium (Hartsock and Nelson, 2008).

5.2. Gut function in OTR KO animals

Additional evidence that OT may be important for gastrointestinal function comes from research assessing the effects of OTR deletion in mice where Welch and colleagues demonstrated that OT signaling regulates gut motility, inflammation, permeability and maintenance of the mucosa (Welch et al., 2014). Enteric neurons and enterocytes within the gut express OTRs (Welch et al., 2014; Welch et al., 2009), suggesting a role for OT signaling in ENS-related gut physiology and function. Accordingly, a whole host of sequela was observed in the gastrointestinal system of OTR KO mice. Compared to WT mice, OTR KO mice were characterized by greater stool mass and water content, as well as higher GI transit time, indicating increased gut motility in the absence of OTRs. In WT mice, OT injections slowed GI transit time, suggesting that OT signaling may serve as a brake on gut motility (Welch et al., 2014). Abnormalities in the intestinal epithelium were also observed in OTR KO mice, including a smaller height in intestinal villi, a smaller crypt depth in the colon and a decrease in proliferating cells within the crypts, suggesting that OT maintains the intestinal wall by regulating the proliferation of transient amplifying cells. Furthermore, OTR KO mice are also characterized by an increase in macromolecular gut permeability, as evidenced by increased diffusion of FITC-dextran dye within the colon wall following oral gavage, as compared to WT mice. Altogether, these results indicate the OT signaling in the mature gut slows gut motility, regulates intestinal permeability and maintains the mucosal epithelium. The observation that OTR KO mice are more susceptible to inflammation (see experimentally-induced colitis models above) than WT mice may have implications for developmental processes that potentially modify OTR expression within the gut.

5.3. Development of OT receptors in the gut

The developmental expression of OTRs suggests that OT signaling may be protective for the gastrointestinal system at birth. OTR mRNA is expressed in neural crest-derived cells isolated from mouse embryonic day (E) 16 gut tissue, demonstrating that precursors that give rise to enteric neurons express OTRs (Welch et al., 2009). In addition, OTR transcripts in the rat intestine are detected as early as E 18, peak at PND 7, remain high at PND 24 and then decline to adult levels that are maintained through PND 56 (Welch et al., 2009). An examination of intestinal tissue at PND 3 reveals that almost all of the neurons within the myenteric plexus of the large and small intestines are OTR-immunoreactive (Welch et al., 2009). Most of these OTR-immunolabeled neurons are also positive for NeuN, a marker of IPANs (see above), although identification of both NeuN nuclear and cytoplasmic staining is difficult at PND 3. In contrast to the myenteric plexus, OTR-ir was first observed in neurons of the submucosal plexus at PND 19. Besides the nerve ganglia of the ENS, OTR-ir was also observed within the mucosal epithelium, such as the intestinal villi and crypts (Welch et al., 2009). At birth (PND 0), enterocytes (epithelial cells) lining the villi are OTR-ir, a pattern that continues until PND 15. At PND 15, however, OTR-ir becomes concentrated at the crypt-villus junctions, with modest OTR-ir in crypt epithelial cells and little within enterocytes (Welch et al., 2009). This concentration of OTRs may signal a role for OT signaling in epithelial cell maturation, crypt cell secretion and/or stability of adherens junctions. While an examination of OT-ir in gut tissue revealed varicose OT-ir fibers surrounding myenteric neurons, clear evidence of a vascular or mucosal innervation by oxytocin neurites was absent and very few enteric neurons displayed OT-ir (Welch et al., 2009). Thus, stimulation of OTRs within intestinal tissue may occur via ENS OT release, ingestion of OT from breast milk (Takeda et al., 1986) and/or hypothalamic release of OT, with the latter being similar to how systemic release of OT from the posterior pituitary stimulates OTRs within uterine tissue for contractions and breast tissue for milk letdown (Welch et al., 2009).

5.4. Protein synthesis, UPR^{ER} and protection to developing enterocytes

For offspring, birth is an adaptive inflammatory/immune event characterized by hypoxic-like conditions (Lagercrantz and Slotkin, 1986; Maron et al., 2010; Tyzio et al., 2006), a surge in stress hormones (Lagercrantz and Slotkin, 1986), elevated fetal cytokines (Castillo-Ruiz et al., 2018a; Golightly et al., 2011), antigen stimulation through gut microbial colonization (Castillo-Ruiz et al., 2018a; Costello et al., 2012) and amino acid insufficiency stress (Klein et al., 2017), with the two latter processes directly impacting the gut. Similar to our speculation that OT may protect fetal *neurons* at birth from cellular stress by modulating protein translation and the UPR^{ER} (Bordt et al., 2019; Klein et al., 2014), we also surmise that OT protects the gut by modulating the exact same processes within fetal *enterocytes*, which line the intestinal villi and show incredibly high expression of OTRs precisely at birth (Welch et al., 2009). As previously mentioned, an increase in cellular stress can lead to a buildup of unfolded and/or misfolded proteins within the ER of cells, resulting in ER stress and activation of the UPR^{ER}. The UPR^{ER}, a cellular stress response, then activates signaling cascades to halt protein synthesis and reduce the protein load in order to restore cellular homeostasis (Hetz, 2012; Hetz et al., 2011; Schroder and Kaufman, 2005b). Several studies by Klein and colleagues demonstrate that OT regulates protein translation and the UPR^{ER} within $Caco_2BB$ cells, a human gut cell line used as an *in vitro* model of enterocytes (Klein et al., 2013, 2014, 2016). Specifically, OT dampens the PI3K/Akt/mTORC1 pathway in cultured $Caco_2BB$ cells by (1) increasing the phosphorylation of Raptor, (2) decreasing the abundance and phosphorylation of S6K1 and (3) downregulating the phosphorylation of $4E\text{-}BP1^{S65}$, all of which serves to decrease protein translation (Kelleher and Bear, 2008). OT also modulates many effector molecules of the UPR^{ER} within $Caco_2BB$ cells, including eIF2a, PERK, IRE1, XBP1 and BiP (Klein et al., 2014), although it is currently unknown whether this is through direct or indirect effects of OT on these molecules. Furthermore, OT induces TRIB3, a protein involved in autophagy (Klein et al., 2014), which is the process of degradation and recycling of cellular components to restore homeostasis.

The findings that OT can modulate effectors of ER stress and autophagy in cultured $Caco_2BB$ cells lead Klein et al. (2016) to examine OT's effects in the presence of low dose LPS stimulation designed to mimic bacterial endotoxin exposure via breast milk in the early

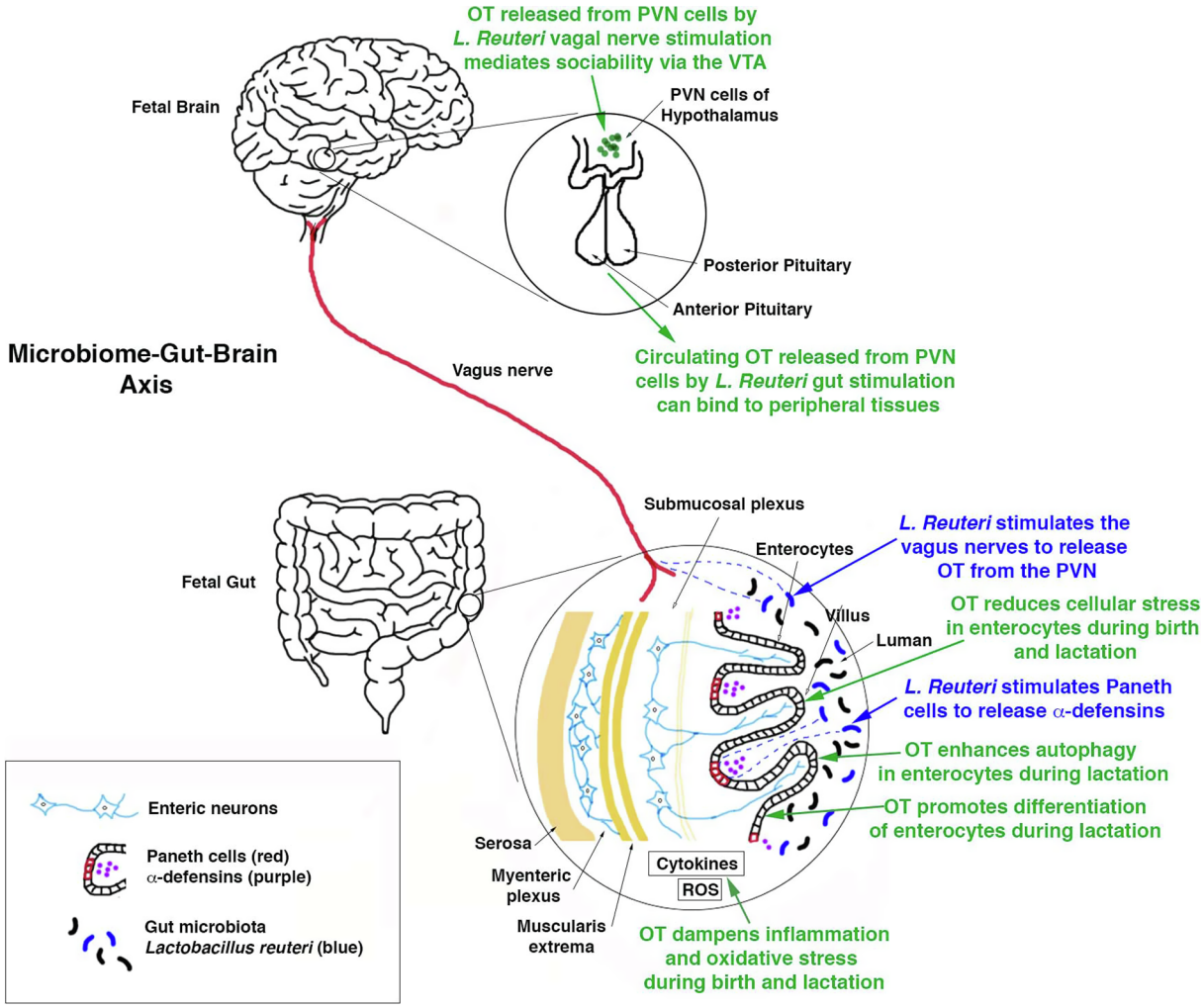

Fig. 1. The microbiome-gut-brain axis illustrating known and proposed roles for OT signaling in the gut and following release via vagus nerve stimulation. We propose that the microbial colonization of the gastrointestinal tract at birth is a highly adaptive and well-coordinated process by which OT released from the paraventricular nucleus (PVN) of the hypothalamus during labor (and subsequently in colostrum and breast milk) modulates intestinal inflammation, cellular stress and autophagy via OTRs that come online during birth and lactation. Furthermore, *Lactobacillus reuteri* (*L. reuteri*), a bacterial species in the gut and breast milk serves as a source of antigen stimulation that regulates the production of the antimicrobial peptides (i.e. α-defensins) and the continued release of OT for proper enterocyte development and immunologic homeostasis. Specifically, *L. reuteri* within the gut stimulates the vagus nerve to release OT from PVN cells and OT binds to oxytocin recpetors on dopaminergic neurons within the ventral tegmental area (VTA) to mediate social affiliation. Circulating OT can also be increased following *L. reuteri* gut stimulation. *L. reuteri*'s combined stimulation of anti-microbial peptides, such as a-defensins, and OT PVN release, ensure normal gastrointestinal development in the presence of continued antigen stimulation by commensal microbes. Roles for OT are illustrated in "green text" while roles for *L. reuteri* are in "blue text." (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

postnatal period. OT inhibited LPS-induced NF-κB signaling/pro-inflammatory cascades and offset LPS's suppression of the UPR^{ER} in $Caco_2BB$ cells. Based on OT's modulation of the various UPR^{ER} signaling components within their model of a physiological stressor (i.e. low dose, low level LPS challenge), Klein et al. proposed that OT in breast milk (1) preconditions enterocytes *in vivo* to resist apoptotic cell death in the presence of low level antigen microbial stimulation and (2) regulates cellular metabolism (including phasic UPR runs) to promote enterocyte cell differentiation (Klein et al., 2016). As a follow-up to the proposed protection mediated by OT in breast milk for newborn intestinal villi, Klein et al. examined the role of colostrum OT on intestinal villi harvested within 6 h of birth (Klein et al., 2017). Within primary cultured intestinal rat villi, colostrum suppresses the UPR^{ER} effector BiP through OTR and regulates protein translation by inhibiting eIF2a and increasing the phosphorylation of eIF2a kinase (pPKR). Colostrum and exogenous OT also simultaneously inhibit NF-κB inflammatory signaling and increase LC3A, a marker of autophagy. Altogether, these findings suggest that colostrum OT protects the fetal gut from cellular stress caused by amino acid starvation in the period between birth and first feeding by (1) dampening inflammation, (2) halting protein translation and (3) enhancing autophagy (Klein et al., 2017). While Klein and colleagues propose that the protective effects of OT on the newborn gut are mediated via OT in colostrum and breast milk, we propose that OT released during labor also protects fetal enterocytes against cellular stress. This is supported by OT's elevation of BiP in intestinal villi that have not yet been exposed to colostrum (Klein et al., 2017), as BiP is an ER resident chaperone protein that helps to clear misfolded proteins (Lee et al., 2003).

5.5. Potential OT feedback loop for the production of anti-microbial peptides and optimal gastrointestinal development

While OT's release from the PVN of the hypothalamus during labor may protect gut enterocytes from inflammation induced by gut microbial colonization and amino acid insufficiency stress at birth, the presence of OT and *Lactobacillus reuteri* (*L. reuteri*) in breast milk may be

part of an adaptive OT feedback loop that ensures normal gastrointestinal development in the presence of continued antigen stimulation by commensal microbes. For example, eight-week old mice treated with *L. reuteri* (isolated from human breast milk) in their drinking water for four weeks showed higher levels of plasma OT, compared to control mice that did not receive the bacteria exposure (Varian et al., 2017). Furthermore, mice treated with postbiotic lysed *L. reuteri* also displayed the increase in plasma OT, as well as a significant increase in OT-immunoreactive neurons in the caudal PVN, suggesting that the ingestion of a bacterial component, peptide or metabolite of *L. reuteri*, rather than the live probiotic bacteria itself, stimulates OT-producing neurons of the PVN, leading to increased circulating OT (Varian et al., 2017). Interestingly, *L. reuteri*-mediated elevation of OT may protect not only gastrointestinal tissue during microbial colonization at birth, but extra-intestinal tissue as well. Within eight-week old mice, *L. reuteri* stimulation of OT via the vagus nerve significantly accelerates wound healing of the skin by activating CD4 + Foxp3 + CD25+ immune T regulatory cells (Poutahidis et al., 2013).

In addition to increasing PVN OT release, *L. reuteri* also stimulates the production of gut antimicrobial peptides that provide defense against pathogens, modify commensal microbial composition and contribute to immunologic homeostasis (Menendez et al., 2013). For instance, the presence of *L. reuteri* in the intestines of mice is associated with increased transcriptional activity of *Defa* genes (specifically *Defa5*, *Defa20*, *Defa 23*), which encode the Paneth cell α-defensin antimicrobial peptides (Menendez et al., 2013). Treatment with antibiotics depleted *L. reuteri* and decreased *Defa5*; *Defa20*, *Defa 23* expression in ileal tissue while addition of heat-killed *L. reuteri* to ileal explants partially restored *Defa* expression (Menendez et al., 2013). Thus, bacterial stimulation by *L. reuteri* elevates *Defa* gene expression, which produces the Paneth cell α-defensins critical for gastrointestinal immune defense and homeostasis. Intriguingly, individuals with ASD, Crohn's disease and necrotizing enterocolitis are not only characterized by gastrointestinal dysfunction and dysbiosis but altered Paneth cell physiology (Gassler, 2017; Horvath et al., 1999). Altogether this research suggests that the microbial colonization of the gastrointestinal tract at birth is a highly adaptive and well-coordinated process by which OT released from the PVN during labor (and subsequently its presence in colostrum and breast milk) modulates intestinal inflammation, cellular stress and autophagy via gut OTRs that come online during birth and lactation while *L. reuteri* in the gut and breast milk serves as a source of antigen stimulation that regulates the production of antimicrobial peptides and the continued release of OT for proper enterocyte development and immunologic homeostasis (Fig. 1). An additional role for *L. reuteri* is the modulation of social behavior through vagal nerve stimulation and central OT release, as described in the next section.

5.6. OT signaling via vagal nerve stimulation (gut-brain axis)

Signaling via the vagus nerve is one of the fastest, most direct routes of gut-brain communication (Fulling et al., 2019) and two recent studies suggest that OT signaling is an integral part of this signaling pathway that gives rise to normal social behavior (Buffington et al., 2016; Sgritta et al., 2019). The vagus nerve is the 10th cranial nerve and serves as a bidirectional route of communication between the viscera and the brain through its paired sensory afferent and motor efferent neurons (Fulling et al., 2019). Importantly, specific bacterial species can activate the sensory vagal afferents that innervate the gut to influence both the brain and behavior (Fulling et al., 2019). In a mouse model of obesity, a maternal high fat diet (MHFD) causes significant deficits in offspring, including reduced sociability, decreased OT production in the PVN, impaired synaptic plasticity in the ventral tegmental area (VTA) and reduced gut microbial diversity, including a significant reduction (greater than 9-fold) in *L. reuteri* (Buffington et al., 2016). Remarkably, the administration of *L. reuteri* to MHFD offspring via their drinking water rescues sociability, OT neuron number in the PVN and synaptic plasticity of VTA dopamine (DA) neurons that are a central part of the mesolimbic reward system. Furthermore, intranasal OT administration to MHFD offspring also rescues VTA plasticity and restores normal social behavior. Thus, Buffington et al. (2016) propose that adequate levels of *L. reuteri* in the gut stimulate vagal afferent fibers projecting to the PVN, resulting in enhanced OT PVN production, as was previously described (Varian et al., 2017). These OT PVN cells, which project onto DA VTA neurons that express OTRs (Melis et al., 2007), then facilitate social interactions through the activation of reward circuitry (Buffington et al., 2016). Activation of this gut-brain signaling cascade by *L. reuteri* is also proposed to restore social behavioral deficits in genetic, environmental and idiopathic models of ASD (Sgritta et al., 2019). For instance, both Shank3B$^{-/-}$ mice and BTBR T+ Itpr3tf/J (BTBR) mice show drastically decreased levels of gut *L. reuteri*, as well as reduced sociability. *L. reuteri* treatment, while having no significant effect on microbiome composition, rescues the social deficits, but only if the vagus nerve is intact. Intranasal OT also rescues the social deficits, even in vagotomized mice. Furthermore, *L. reuteri* restores the VTA synaptic plasticity that drives the increased sociability in Shank3B$^{-/-}$ mice. However, in mice lacking OTRs within DA neurons, neither *L. reuteri* nor OT treatment rescues the VTA DA synaptic plasticity or sociability. In summary, within both the MHFD and ASD mouse models, *L. reuteri* rescues social behavior deficits via gut-brain communication that includes the vagus nerve, PVN OT, and VTA DA neurons that express OTRs (Buffington et al., 2016; Sgritta et al., 2019). Thus, events at birth that alter gut inflammatory processes, such as a decrease in protective OT signaling, a lack of breast feeding, antibiotic use, MHFD, etc. may deplete *L. reuteri*, thereby altering gut-brain communication and emergent social behaviors. Interestingly, IP injections of OT or an OTR antagonist 24 h after birth in prairie voles causes a significant increase in OT PVN immunoreactivity on PND 21 in females but not males (Yamamoto et al., 2004), indicating that exogenous manipulations of OT signaling near birth have the potential to alter the OT circuitry implicated in the proposed vagal-PVN-VTA pathway that modulates sociability, with sex-specific effects.

6. Manipulations of OT signaling at birth relevance of birth interventions

6.1. Administration of Pitocin (synthetic OT)

Given all the protective effects of endogenous OT signaling at birth, one might imagine that the administration of synthetic OT (sOT; Pitocin) to pregnant women for labor induction and/or augmentation might provide similar or even enhanced protection to the developing fetal brain and gastrointestinal tract. This is an especially important concept to consider given that 23–50% of pregnant women in the United States currently receive sOT to induce or augment labor (Declercq et al., 2014; Hamilton et al., 2014) and very little is known about the long-term consequences of such interventions for offspring. In contrast to a protective role, several studies have reported that sOT administration at birth for labor induction and/or augmentation is associated with an increased risk of attention deficit hyperactivity disorder (Tsimis, 2013), ASD (Friedlander et al., 2017; Gregory et al., 2013; Smallwood et al., 2016) or pervasive developmental disorder (PDD) (Polo-Kantola et al., 2014), the latter of which is a diagnosis given to individuals that do not fully meet the criteria for ASD but whose symptoms closely resemble those with ASD. One possible explanation for these associations is oxytocin-induced receptor desensitization whereby continuous exogenous OT exposure causes a decreased responsiveness to OT and the internalization of OTRs within the brain and gut, as has been shown for uterine tissue (Plested and Bernal, 2001; Robinson et al., 2003). Another explanation for the association may be the promiscuous binding of OT to vasopressin receptors following the administration of high levels of exogenous OT (Song and

Albers, 2018), as signaling through the V1a receptor (present in the brain and gut) can be pro-inflammatory (Bordt et al., 2019) and exacerbate neuronal damage under conditions of hypoxia/hypoglycemia (Tanaka et al., 1994) (but see (Spoljaric et al., 2017). However, as noted by Gregory et al. (2013), despite controlling for potential confounders, the increased odds of having a child with ASD following labor induction and/or augmentation could be due to (1) maternal pre-existing pregnancy conditions that make it more likely that a woman requires sOT during labor or (2) the events of labor associated with induction/augmentation, rather than (3) the administration of sOT *per se*. Gardener et al. (2011) further suggest that autistic fetal development prior to birth or familial factors may also underlie the association between autism and obstetrical or neonatal complications.

However, other studies have found no positive association between sOT administration at birth and an increased risk of ASD (Polo-Kantola et al., 2014; Mamidala et al., 2013), including a recent study specifically examining the dose-dependent effects of sOT exposure on disease risk, although a significant relationship was found between sOT dose and offspring rating on the Child Behavioral Checklist (CBCL; assessment of behavioral and emotional problems), with a 3% increase in odds of CBCL morbidity with each 1 unit increase in sOT during labor (Guastella et al., 2018). Interestingly, within an *in vitro* rodent model of hypoxia-ischemia, OT's protection of neural tissue at birth is concentration dependent and characterized by an inverted U-shaped curve with a medium sOT dose (1 μM) conferring the most neuroprotection while higher (10–100 μM) and lower doses (100 nM) decrease cell viability (Ceanga et al., 2010). Along these lines, dose-dependent effects of OT have been described for social behavior in prairie voles (Carter, 2017b). A low dose of OT given to prairie voles shortly after birth increases pair bond formation while higher doses impairs pair bonding. In females, high OT doses switch their innate preference from their partner to strangers (Bales et al., 2007). A study by Gardener et al. (2011) examined over 60 perinatal and neonatal factors in a meta-analysis and found that the collection of obstetrical complications that confer the greatest risk for ASD (growth retardation, fetal distress, resuscitation, meconium aspiration and Cesarean delivery) suggest a role for fetal/neonatal hypoxia as a common denominator. Given OT's prominent protective role against hypoxic-like conditions at birth, further research is needed to examine the effects of endogenous maternal OT release compared to exogenous sOT administration at birth, included sOT dose-dependent effects. Animal models may prove useful in this regard as these models can mechanistically investigate how sOT dose during labor impacts the brain, gut and behavior of offspring, while eliminating potential confounders that are either difficult to control or hard to identify within humans (i.e. maternal and fetal pre-existing conditions, adverse events during labor, etc.).

6.2. Elective Cesarean delivery

It is also important to consider whether birth by elective C-section alters the developmental trajectory of nervous and gastrointestinal system development in offspring given the protective nature of endogenous OT signaling at birth and the fact that these deliveries occur without endogenous OT-mediated labor. Elective C-sections, as we discuss them here, are non-emergency cesarean deliveries that are planned, unlabored deliveries. To specifically asses how an absence of OT signaling at birth might impact development, this type of C-section should also not be "indicated" due to pre-existing maternal or fetal conditions (potential confounders), although this detail is often not noted in studies, is unknown, or refers to both indicated and "by choice" elective/planned C-sections. Nevertheless, one third of US woman give birth by C-section (Hamilton et al., 2014; Zhang et al., 2010) with more than half of these C-sections as elective or planned pre-labor deliveries (Zhang et al., 2010), during which fetal OT exposure is reduced due an absence of spontaneous labor (Marchini et al., 1988). Interestingly, a recent study in rodents reported a significant reduction in widespread neuronal cell death in the postpartum period of vaginally born mice, as compared to mice born via unlabored C-section, suggesting a protective effect of a labored vaginal birth for neuronal viability (Castillo-Ruiz et al., 2018b).

Human studies investigating a positive association between elective C-sections and ASD in offspring have yielded mixed results. To date, several studies have reported an increased risk for ASD (Curran et al., 2015a,b; Yip et al., 2017) or PDD (Polo-Kantola et al., 2014) following elective C-sections, compared to vaginal deliveries. In an analysis by Yip et al. (2017), the positive association between planned C-sections and ASD risk remained significant for *at term* births across 5 study sites (Demark, Finland, Norway, Sweden and Western Australia), in addition to the positive association observed for preterm births. While Polo-Kantola et al. (2014) found no association between planned C-sections and childhood autism or Asperger syndrome, they did find an association for PDD and planned C-sections, but not emergency/urgent C-sections, the former of which would be characterized by low OT exposure due to a lack of labor (Marchini et al., 1988). Curran et al. (2015) reported a 21% increased risk for ASD following elective C-sections, compared to unassisted vaginal delivery, based on 2.7 million deliveries. However, further examination using 2,555 sibling pairs discordant for ASD and delivery mode failed to show a causative link between C-section and ASD (Curran et al., 2015a), suggesting that additional genetic or environmental risk factors contribute to the association.

It may be that planned C-sections create a neural vulnerability for ASD that is unmasked by additional risk factors or that confounding factors, such as anesthesia type (regional vs. general), antibiotic use, maternal pre-existing conditions, familial factors, environmental factors, etc. drive the association between ASD and cesarean delivery. For instance, compared to vaginal deliveries, planned C-sections may reduce endogenous OT exposure that normally protects the fetal brain and gut from inflammatory processes at birth, with additional vulnerabilities being an alteration in the normal gut microbiome colonization due to delivery mode (Azad et al., 2013; Backhed et al., 2015; Moya-Perez et al., 2017), antibiotic use at the time of C-section (Azad et al., 2016), and an absence of breastfeeding that deprives the gut of further OT protection, stimulation by *L. reuteri* and adequate production of α-defensins. Indeed, continued breastfeeding following C-section/intrapartum antibiotic treatment can foster a gut microbiome that is similar post-weaning to that found in vaginally delivered offspring without antibiotic exposure (Azad et al., 2016). Interestingly, individuals with ASD are characterized with gastrointestinal disturbances, dysfunction and/or disease (Isaksson et al., 2017; Valicenti-McDermott et al., 2006), altered gut microbiota and reduced gut diversity (Kang et al., 2013), and immune dysfunction (Hsiao, 2013), in addition to the well-known sensory, cognitive and social behavioral deficits. Besides ASD, studies have reported offspring born via elective C-sections are at greater risk of developing immune disorders such as asthma, allergies, type 1 diabetes and celiac disease (Cho and Norman, 2013). Furthermore, type of anesthesia may synergize with a Cesarean delivery to create additional risk for ASD. Compared to vaginal deliveries and C-section deliveries with regional anesthesia, C-section deliveries with general anesthesia are associated with a greater risk for ASD, particularly for girls (Chien et al., 2015). Chien et al. (2015) suggest that this finding may be due to how each type of anesthesia affects tissue perfusion since regional anesthesia causes vasodilation and increases tissue oxygenation (Treschan et al., 2003) while general anesthesia produces vasoconstriction and reduces tissue oxygenation (Buggy, 2000). Because endogenous OT released during labor protects the brain against hypoxic-like conditions where tissue is deprived of oxygen (Tyzio et al., 2006; Khazipov et al., 2008), both by inducing the switch in GABAergic signaling in neurons and augmenting epinephrine levels that shunt blood supply to vital organs, the combination of an unlabored C-section with general anesthesia may make the fetus particularly vulnerable to neural insults arising from reduced tissue

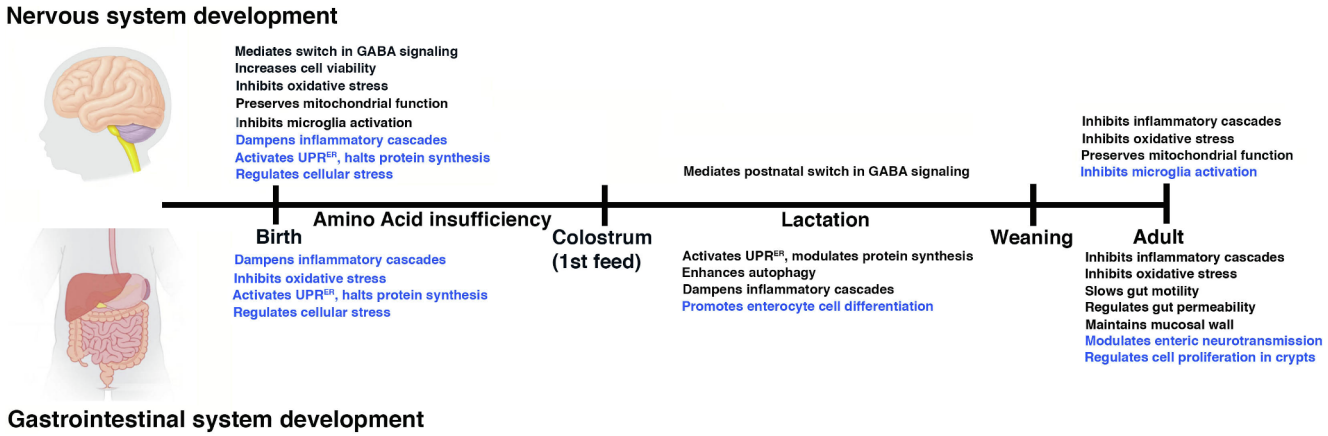

Fig. 2. Proposed roles for OT signaling for the fetal brain and gastrointestinal system at birth and during postnatal development into adulthood based on animal models. The OT functions listed in "black text" indicate known roles for OT based on *in vivo* and/or *in vitro* studies and OTR knockout animals. The OT functions in "blue text" are hypothesized roles for OT at different developmental time-points. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

perfusion, reduced OT exposure and reduced epinephrine levels.

7. Factors influencing sex-specific risks versus resilience in relation to OT signaling at birth

ASD is more prevalent in boys than girls, with 3–4 males affected for every female (Baio, 2010; Loomes et al., 2017), suggesting that boys may be more vulnerable to genetic and/or environmental risk factors. Here we discuss how sex differences may create an enhanced vulnerability for males during birth, compared to females, particularly in reference to OT's functions at birth. As described earlier, elevations in OT just before birth protects the fetal brain from the hypoxic-like conditions of delivery by mediating an excitatory to inhibitory switch in GABA signaling within neurons (Tyzio et al., 2006). This OT-mediated switch in GABA signaling blocks the NKCC1 cotransporter and prevents the elevation of intracellular $[Cl^-]_I$, thereby reducing the metabolic demand of neurons (Tyzio et al., 2006; Khazipov et al., 2008). Interestingly, circulating testosterone in males becomes elevated just before birth due to increased testicular function and is aromatized to estradiol in neurons (McCarthy et al., 2002). McCarthy et al. (2002) describe how estradiol in males then functions to (1) increase the excitatory action of GABA at various brain sites and (2) extend the developmental duration of GABA's depolarizing actions in the perinatal period. As shown by Tyzio et al. (2014), a failure to switch GABA signaling from depolarizing to hyperpolarizing during the narrow window of delivery causes abnormal postnatal neuronal hyperexcitability and autistic-like behavior in offspring. Thus, males with their enhanced depolarizing action of GABA, may be particularly vulnerable to alterations in OT signaling at birth that prevent the depolarizing to hyperpolarizing switch.

There may also be sex differences in mitochondrial function at birth that make males more susceptible to hypoxic-like events. As previously mentioned, OT reduces oxidative stress and preserves mitochondrial function in the context of a OGD paradigm that models hypoxia-ischemia (Kaneko et al., 2016), which suggests that OT may protect mitochondrial function during the hypoxic-like conditions of birth (Lagercrantz and Slotkin, 1986; Khazipov et al., 2008). In cases of extreme hypoxia where the brain is deprived of oxygen and blood flow for a defined period of time during birth, individuals can develop neonatal hypoxic-ischemic encephalopathy (HIE), a disorder characterized by intellectual disabilities, cognitive impairment, developmental delays, cerebral palsy and epilepsy (Conway et al., 2018). For this disease, males are typically more intellectually impaired than females (Smith et al., 2014). To further investigate this sex difference, Demarest et al. (2016) exposed neonatal rats on PND 7 to neonatal hypoxic-ischemia (HI) and then assessed mitochondrial function and levels of oxidative stress. Compared to females, male rats displayed impairments in mitochondrial respiration, a reduction in mitochondrial GPx antioxidant activity and a 3–4 fold increase in oxidative protein carbonylation (a direct measure of oxidative damage by ROS accumulation) following HI (Demarest et al., 2016). Within the sham (i.e. baseline) condition, female rats had ~30% more GSH than males. Furthermore, following HI, GSH levels in females were reduced to the levels in sham males, suggesting that females normally possess greater antioxidant capacity than males and this may explain the sparing of their mitochondrial function (Demarest et al., 2016). Thus, if there is a reduction in OT at birth that creates an increased vulnerability to the hypoxic-like conditions of delivery, particularly in the instances of a difficult birth, males may be at greater risk of neurological damage due to innate sex-differences in mitochondrial function and antioxidant capacity. Along these lines, mitochondrial dysfunction and enhanced oxidative stress is increasingly recognized as a major player in intellectual disability-related disease, such as ASD, Fragile X syndrome, Down's syndrome and Rett syndrome, (Palmieri and Persico, 2010; Valenti et al., 2014), with the three former diseases characterized by a male sex bias, raising the question as to how mitochondrial function might be related to disease pathology.

8. Conclusions

Birth is a highly adaptive yet stressful experience and is perhaps one of the most significant life events for both a mother and child. Humans and other species of animals have evolved complex, integrated physiological mechanisms to facilitate the transition of the fetus to an extrauterine environment. In the present review, we examined the specific functions of oxytocin signaling at birth beyond its well-known roles of the stimulation of uterine contractions and milk letdown, describing how it is also important for fetal lung maturation and fetal analgesia. We then explored in depth the role of OT for the fetal nervous and gastrointestinal systems at birth, given that birth is a significant inflammatory event for the brain and gut and OT is a powerful anti-inflammatory molecule (Fig. 2). For the fetal brain, OT is neuroprotective at birth by mediating a switch in GABA signaling that protects neurons from hypoxic-like conditions. OT also appears to inhibit oxidative stress, preserve mitochondrial function and inhibit microglia activation. We propose additional neuroprotective functions of OT at birth that includes the inhibition of inflammatory cascades and a reduction in cellular stress through activation of the UPR^{ER} and a halt in protein translation. Within the intestinal tissue of offspring, we speculate that OT provides protection by dampening inflammatory cascades, limiting oxidative damage, and regulating cellular stress through modulation of

the UPR^{ER} and protein translation (Figs. 1 and 2). Many of these roles for OT have been proposed to be important for enterocytes in the early postnatal period during lactation. We also describe exciting new studies showing OT's relevance for the microbiome-gut-brain axis and how vagal nerve stimulation by the gut bacteria *L. Reuteri* may mediate social behavior and be part of a positive feedback loop for continued OT production that ensures normal gastrointestinal development in the presence of continued antigen stimulation by commensal microbes. Given that many pregnant women undergo interventions that involve the manipulation of OT signaling during delivery, further research is required to investigate how the effects of endogenous maternal OT release compare with the administration of exogenous sOT administration at birth, including sOT dose-dependent effects. Similarly, the effects of planned elective C-sections require further investigation given that they limit fetal OT exposure and produce alterations in the infant gut microbiome due to a lack of vertical transmission of maternal gut bacteria that naturally occurs during a vaginal birth. Given the multitude of physiological processes that OT likely coordinates at birth, we suggest that modifications of this signaling system have the capacity to alter developmental trajectories in both the nervous and gastrointestinal systems to influence offspring health and behavior.

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