Review article

Perspectives of Pitocin administration on behavioral outcomes in the pediatric population: recent insights and future implications

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ABSTRACT

Oxytocin plays an important role in the regulation of parturition as this peptide hormone promotes uterine smooth muscle contractility in gravid women undergoing labor. Here, we review the impact of Pitocin administration on behavioral outcomes in the pediatric population. Pitocin is a synthetic preparation of oxytocin widely used in the obstetric practice for the management of labor and postpartum hemorrhage. We begin by tracing the neuroanatomy of oxytocin-containing cells from an evolutionary perspective and then summarize key findings on behavioral and neural activity reported from offspring dosed with Pitocin during vaginal delivery. Finally, we discuss future directions that are experimentally tractable for understanding the developmental consequences of Pitocin administration on a small but growing subset of children worldwide. Given that fetal past experiences can shape the future behavior of the adult, further work on oxytocin signaling pathways will provide valuable references and insights for early-brain development and state-dependent regulation of behavioral outcome.

1. Introduction

Human pregnancy is a complex physiological event in which several proteins are synthesized, secreted, transferred and ultimately metabolized by maternal organs under tightly regulated processes sculpted by years of hominin evolution. An important molecule that circulates in the plasma proteome during pregnancy is oxytocin, an evolutionary conserved nine amino-acid peptide whose ancestral analogs can be traced back to the time when protostomes and deuterostomes diverged in embryonic development approximately 600 million years ago (Douzery et al., 2004; Liutkeviciute et al., 2016).

The long evolutionary trajectory of oxytocin and the restrictive convergence of pregnancy in mammals, has sculpted oxytocin to assume a key role in parturition, more specifically, in signaling the female uterus to rhythmically contract and relax to enable the fetus to emerge from the vagina (Voltolini and Petraglia, 2014; Kim et al., 2017). This ancient regulated parameter in pregnancy has nowadays been usurped by modern medicine in the form of timed labor induction, labor augmentation and third stage labor management through the use of synthetic oxytocin agonists such as Pitocin (Kimura et al., 2013; Kenkel et al., 2014; Page

et al., 2017). Although the judicious use of Pitocin has obvious clinical benefits, it is far from clear what the potential consequences of this drug intervention are for the neonate. In this review, we discuss what we currently know about the increased use of exogenous oxytocin on the physiology and behavior of drug-exposed offspring. Along the same lines, we propose several developmental outcomes that could emerge from the intravenous administration of Pitocin, particularly in nascent networks of genes and proteins regulated by endogenous oxytocin signaling pathways.

2. Neuroanatomy of oxytocin-containing cells

Oxytocin is synthesized by magnocellular neurons located in the paraventricular (PVN), supraoptic (SON), and accessory nuclei of the anterior hypothalamus (Figure 1A). These neurosecretory cells are the main sources of oxytocin in the mammalian brain (Torres et al., 1992). The long axons of these neurons branch extensively to various parts of the brain, with particular dense branching seen within the amygdala and the posterior pituitary gland where oxytocin molecules are stored in dense-core vesicles for subsequent secretion into the general circulation
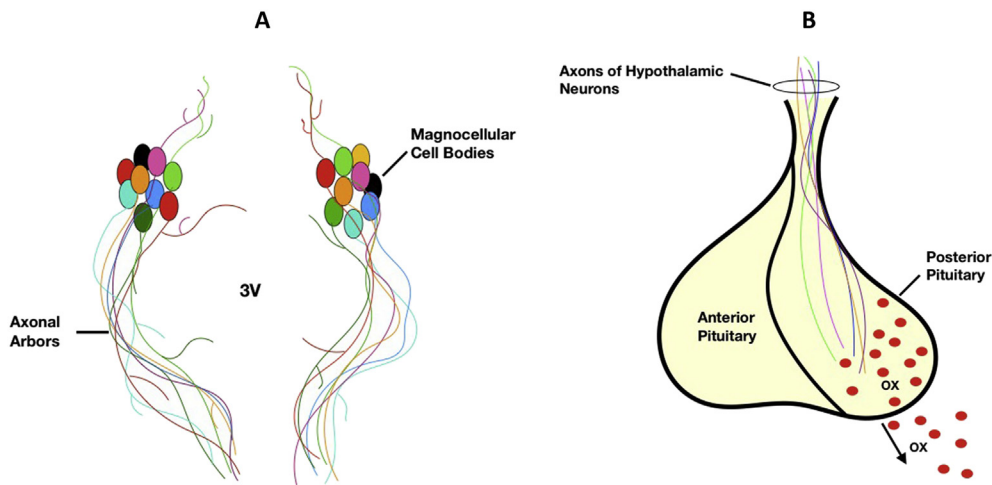

Figure 1. Schematic diagrams depict the synthesis and secretion of oxytocin molecules in the mammalian brain. Oxytocin is synthesized by neurons in the anterior hypothalamus (A). The long axons of these neurons extend to the posterior pituitary gland (B) where oxytocin is secreted into the general circulation *via* the neurohypophyseal capillary plexus (black arrow). It should be noted that oxytocin (OXT) secretion can be regulated locally by neurotransmitters and other molecules traveling to the same cell territories covered by oxytocin axonal arbors. Although oxytocin is also produced in the SON, this particular hypothalamic nucleus is the main source of plasma arginine-vasopressin (AVP). OXT and AVP derived from the SON are involved in several functions within the CNS as neurotransmitters or neuromodulators (Ishunina and Swaab, 2002). To help determine the relative position of the anterior hypothalamus, the third ventricle (3V) is depicted herein.

(Figure 1B). Oxytocin is therefore a neurohypophysial hormone whose information-coded signals are transmitted *via* the oxytocin receptor (located on chromosome 3p25.3), a cell membrane-bound receptor which belongs to the rhodopsin-type (class I) G protein-coupled receptor family (GPCR; Jurek and Neumann, 2018). Oxytocin GPCR polymorphic variants (e.g., rs53576, rs2254298) are ubiquitously located throughout the brain and body as mRNA species for the aforementioned GPCRs are detected in limbic regions of the brain, spinal cord, heart, gastrointestinal tract, adrenal tissue and uterus, for example (Hammock and Levitt, 2013; Greenwood and Hammock, 2017). Thus, during the expulsive phase of parturition, oxytocin signaling cues from the maternal anterior hypothalamus, the fetal-placental unit and the chorion-decidua connectome converge simultaneously upon myometrial cells regulating uterine contractions to expel the fetus through the birth canal (Yulia and Johnson, 2014). Under this unique physiological event, oxytocin signaling is dynamic, state dependent and task dependent.

3. Evolution of oxytocin signaling pathways

It should be noted that the actions of oxytocin are not only confined to uterine contraction, but also in modulating certain aspects of mammalian social behavior such as parental care, heterozygous pair bonding and homophily cooperation (Carter, 2014; Miller and Caldwell, 2015). How does oxytocin contribute to such varied behaviors is the subject of ongoing investigation. Regardless, as previously mentioned in the Introduction, oxytocin has had a long evolutionary history as this hormone and its structurally similar hypothalamic hormone, arginine-vasopressin (both located on chromosome 20p13) evolved from gene duplication of the ancestral molecule, vasotocin, approximately 600 million years ago (Liutkeviciute et al., 2016). As gene duplication is the primary mechanism for acquiring new DNA sequences and creating genomic novelty in eukaryotes, it is thought that the shaping of oxytocin signaling during evolution, particularly the evolution of protostomes and deuterostomes led to oxytocin-like genes assuming new roles in reproductive physiology (Gruber, 2014). In this context, the evolution of oxytocin signaling is an interesting archetype of modular-binding proteins involved in various fundamental functions across taxa and time-scales. For example, although protostomes (to which most invertebrates belong) and deuterostomes (to which some invertebrates and all vertebrates belong) evolved independently, the peptide coding sequences of vasotocin, inotocin and oxytocin have conserved their basic amino-acid structure (Grimmelikhuijzen and Hauser, 2012). For instance, comparison of the coding sequences between the

aforementioned three peptides shows one amino-acid substitution between oxytocin and the ancestral nona-peptide, vasotocin, whereas three amino-acid substitutions are noted between oxytocin and the invertebrate version of oxytocin, inotocin (Figure 2). This foreground comparison demonstrates how an ancient subset of peptides having diverse biological functions and distributed broadly across different taxa have evolved to modulate uterine smooth muscle contractility in vertebrate, mammalian and hominin pregnancies (Grimmelikhuijzen and Hauser, 2012).

4. Exposure to oxytocin agonists *in utero*: implications for health outcomes

Pitocin is widely used in obstetric care to induce and augment labor. For example, approximately 50% of laboring women in the US are dosed
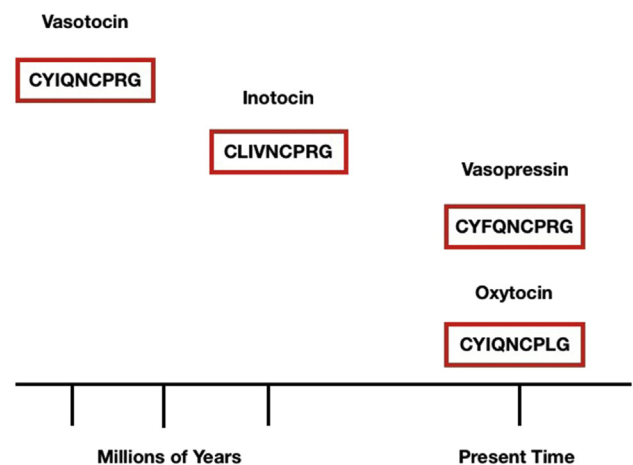

Figure 2. Schematic diagram depicts the amino-acid sequence of four related nona-peptides that emerged through gene duplication events (only main features are shown). Phylogenetic comparative methods based on phylogenic trees and trait measurements of extant species suggest that oxytocin-like peptides (e.g., vasotocin) originated approximately 640–760 million years ago. Peptide signaling is therefore an ancient pathway involving juxtacrine, paracrine, endocrine and neuronal signaling in early arthropods (e.g., inotocin; Stafflinger et al., 2008) and present day mammals (e.g., vasopressin and oxytocin). Circulating arginine-vasopressin and oxytocin hormones affect the physiologic function of peripheral organs such as the kidney, mammary gland and the uterus.

with Pitocin to stimulate contractions and to control postpartum hemorrhage (Arrowsmith and Wray, 2014; Page et al., 2017). As early exposure to drugs is thought to affect the developing fetus, it is reasonable to suspect that exposure to Pitocin might impact cellular pathways that determine the wellbeing of the perinatal child (Figure 3; Kenkel et al., 2014; Lønfeldt et al., 2019). This particular reasoning is important because there is limited information regarding the physical embodiment and health consequences of synthetic oxytocin in the obstetric population.

Pitocin is administered intravenously at doses of 0.5–1 mU/min, with gradual increments of the drug (1–2 mU/min) administered every 30–60 min until uterine contractility yields a labor phase of cervical dilation of 5–6 cm (Kernberg and Caughey, 2017). In low-risk women, the mean length duration of active labor (first and second stages) is around ~7 h for nulliparous women and approximately ~6 h for multiparous women (Albers, 1999). It is during this time of Pitocin administration that fetuses are indirectly exposed to ~6 mL of synthetic oxytocin per hr (assuming 20 U Pitocin in 1000 cc D5LR). The half-life of Pitocin is relatively short (~10–12 min) and in the periphery, Pitocin is most likely metabolized by the same enzyme that inactivates endogenous oxytocin: placental leucine aminopeptidase, a membrane-bound enzyme also expressed in magnocellular neurons of the anterior hypothalamus (Tobin et al., 2014; Bernstein et al., 2017). Against this background, much of what we know about the studied subject is based on rodents, as these animals afford a higher degree of experimental manipulation and observation than humans (Kenkel et al., 2014). Irrespective of whether animal findings might (or might not) have relevance across species, very little information is available on the effects of Pitocin either at the time of exposure (i.e., perinatal period) or long after drug exposure (i.e., postnatal period). The few retrospective human studies available suggest negative consequences of Pitocin exposure on spontaneous suckling reflexes, breastfeeding outcomes and pre-feeding cues during infant development (Bell

Figure 3. Schematic diagram depicts how the administration of Pitocin during critical periods of heightened environmental sensitivity might affect infant behavior. Although the effects of exogenous oxytocin may happen during the fetal state, the repercussions of this hormonal exposure may occur much later in adulthood and perhaps across several generations. We propose various experimental strategies that incorporate the evolutionary history of oxytocin into systems-level analyses of health and disease. The impact of early experience on social, perceptual and cognitive systems has important implications for understanding allelic variation, chromatin modification, neural network activities and local environmental cues.

et al., 2013; García-Fortea et al., 2014; Brimdyr et al., 2015; Marín Gabriel et al., 2015; Erickson and Emeis, 2017; Fernández-Cañadas Morillo et al., 2017, 2019; Gomes et al., 2018). Along the same lines, Pitocin-treated infants appear to exhibit relatively low APGAR scores in muscle tone, heart rate, breathing, reflex responses and deficits in gross and fine motor development (González-Valenzuela et al., 2015). There are also reports suggesting that perinatal Pitocin use may increase the risk of infants developing Attention Deficit/Hyperactivity Disorder, Autistic Disorder and increasing the rates of neonatal morbidity (Kurth and Haussmann, 2011; Buchanan et al., 2012; Weisman et al., 2015). However, there is also a number of mostly retrospective studies showing no significant side-effects or adverse events in the studied populations, with most studies referring to administration of Pitocin around the time of labor being well tolerated by the infant (Henriksen et al., 2015; Gottlieb, 2016; Stokholm et al., 2018; Lønfeldt et al., 2019). Finally, as far as the authors are aware, no studies have evaluated single-nucleotide polymorphisms within the oxytocin receptor genes in an attempt to correlate Pitocin exposure with infant behavioral outcome. This is an important correlation as associations of oxytocin receptor variants and Autism Spectrum Disorders have been reported using IQ tests and Vineland Adaptive Behavior Scales (Lerer et al., 2008). Taken together, these broad and diverse studies show a lack of clear consensus on whether Pitocin exposure has a reliable and reproducible effect on postnatal brain development and by extension on cognitive skills, psychomotor behavior and/or specific neural substrates underlying psychiatric disorders. The discrepancies and uncertainties highlighted above may be explained in part by the difficulty of retrospective studies, as differences in independent variables such as dose of Pitocin, timing of Pitocin administration and behavioral endpoints measured could result in very different experimental outcomes. We conclude therefore that oxytocin supplementation during labor may have discrete and modest effects on peptide signaling pathways underlying infant behavior.

5. Discussion

It is becoming clear that oxytocin administration around the time of labor may lead to short-term changes in postnatal behavior. As the brain is the anatomical skeleton for cognition and behavior, it would seem that Pitocin targets oxytocin-sensing neurons through a direct signaling mechanism to affect sensory coding and behavioral output. However, Pitocin has only a limited effect on the fetal or adult brain. The synthetic molecule is too large (and hydrophilic) to penetrate the blood-brain barrier to directly reach neurons bearing the oxytocin receptor. Yet, it is conceivable that the effects of oxytocin outside the brain influence behavior within the brain. Indeed, there is a lot of evidence suggesting that peripheral or systemic activity may be a driver of mammalian behavior. For example, although the lamina terminalis within the anterior hypothalamus monitors thirst and drinking behavior, activation of a gastrointestinal-based circuit is required for thirst-sensing neurons to drive thirst reduction (Augustine et al., 2019). Similarly, although the adipocyte-derived hormone leptin signals the arcuate nucleus and PVN of the hypothalamus about food intake, it is activation and secretion of corticosterone from the adrenal cortex that is initially required to fully increase hunger states (Perry et al., 2019). These two endocrine examples convincingly show that peripheral activity is an under-appreciated step in homeostatic regulation of hypothalamic neurons. Thus, an intervening endocrine step for the actions of oxytocin in the periphery might also be required to successfully drive signaling mechanisms to the fetal brain. Indeed, secretion of glucocorticoids (e.g., cortisol) from the adrenal gland inversely affect the synthesis of oxytocin levels in the human and rodent brain (Sanders et al., 1990; Windle et al., 2004; Jurek et al., 2015). The observed cortisol-oxytocin interaction offers quantitative evidence for the biological proposition that peripheral or systemic activity can impact neuronal function by modulating membrane excitability and/or synaptic connections (Neumann, 2002). As well known, cortisol and corticosterone are steroid hormones secreted in response to stress-related
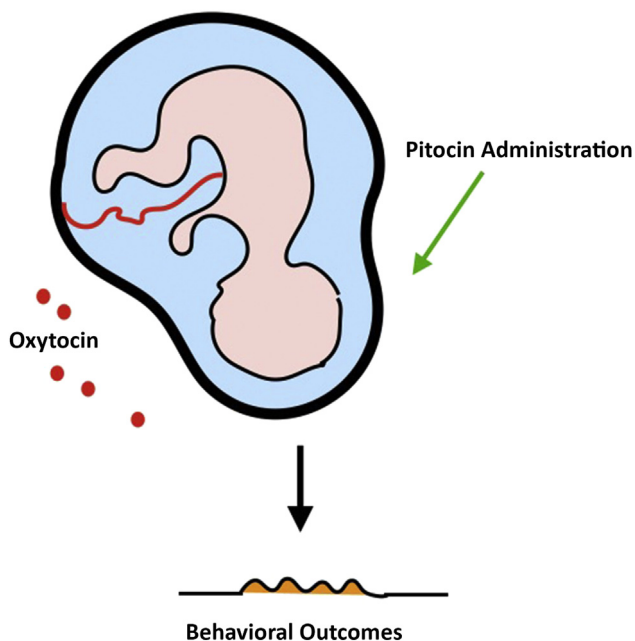
disorders. To accomplish this particular task, cortisol penetrates the brain parenchyma where it targets in particular the amygdala complex whose neurons are sensitive to cues that signal distress. The contextual actions of cortisol in the brain are mediated through ligand activation of intra-cellular nuclear mineralocorticoid receptors expressed in amygdala cell networks. Thus, cortisol signaling from the fetal adrenal cortex which is already functional by the 22 week of gestation (Weinstock et al., 1992), may indirectly convey specific references related to the administration of Pitocin to neural circuits generating early-life behavior. These studies collectively suggest that additional sources of oxytocin in the periphery can broadcast state signals to large ensembles of neurons *via* local endocrine activity or through vagal afferent activity, as this cranial nerve can acutely detect oxytocin levels to subsequently inform the fetal brain about internal drives and growth environments (Carter, 2014).

6. Open questions

The fetal experience within the womb is a complex physiological and behavioral process, each with distinct causal mechanisms and outcomes for the offspring. While it is generally thought that maternal behavior is correlated with fetal outcome, many fundamental questions about the impact of Pitocin administration on the human fetus remain unsolved. Here we highlight some of the key unanswered questions.

6.1. Trans-generational epigenetic phenomena in fetuses exposed to Pitocin

A survey of the clinical and experimental literature suggests that fetal past experiences can shape the future behavior of the adult. It is thought that such experiences must leave some enduring imprint on the developing brain, modifying neural circuits related to cognitive skills and ultimately contributing to individual differences (Grewen et al., 2010; Sweatt, 2019). The many facets of the oxytocin system in the brain point to this ancient peptide system in conveying the imprint of the fetal experience through epigenetic mechanisms (Puglia et al., 2015; Krol et al., 2019). Epigenetics refers to heritable changes in gene expression broadcasted through meiosis and mitosis that are independent from any underlying change in DNA sequence (Sarkies, 2019). The major epigenetic mechanisms include DNA methylation, histone protein modification and silencing of micro-RNAs which are thought to initiate, sustain and propagate the effects of the fetal experience across several generations. Oxytocin exposure at birth appears to be associated with epigenetic phenomena as methylation of the oxytocin GPCR in the fetal nervous system can result in long-term changes in behavior, including behaviors that have traditionally been linked to endogenous oxytocin signaling (e.g., social affiliative behavior; Maud et al., 2018; Kenkel et al., 2019). The growing appreciation of receptor methylation in model organisms and humans (Kimmel et al., 2016; Toepfer et al., 2019; Krol et al., 2019) raises plausible hypotheses about how Pitocin administration during labor might impact not only drug-exposed F1 fetuses but also F2 offspring carrying the epigenetic experience of Pitocin. For example, if Pitocin administration augments multiple outcome measures of sociality, this could theoretically lead to increased gregariousness and relaxation of the stress response; positive behavioral traits with important evolutionary implications (Bell et al., 2014; Sweatt, 2019). The possibility that favorable outcomes from Pitocin administration might have benefits across generations is a topic of significant interest, and one that deserves further experimental detail (Feldman et al., 2016; Mitre et al., 2018). Finally, it should be noted that Pitocin might also affect the behavior of offspring through changes in maternal physiology and/or behavior, including postpartum phenomena, stress and pain, lactation and filial attachment (Bell et al., 2014). The fact that epigenetics and maternal experiences can potentially affect fetal neurons indicates that neither

process can necessarily be considered separately. Perhaps, charting the developmental patterns of each process will be important for understanding the expected benefits and risks associated with Pitocin administration in modern obstetrics.

6.2. Impact of Pitocin administration on neonatal breathing behavior

While one of oxytocin's important properties is its oft-cited ability to act on the uterus, oxytocin has much more expansive, active and, at times, subtle, roles within the fetal brain. One of these properties is the ability to switch the polarity of γ-aminobutyric acid (GABA) signaling from depolarizing (i.e., excitatory) to hyperpolarizing (i.e., inhibitory) mode (Tyzio et al., 2006). Depolarization is a neural activity in which polymodal ion channels allow certain ions (e.g., Na^+ and K^+) change the membrane potential thus increasing the strength of synaptic transmission. In contrast, hyperpolarization is a mechanism in which $GABA_A$ ionotropic channels keep intracellular Cl^- levels low through the activity of cation-chloride co-transporter proteins thus blocking synaptic transmission (Schulte et al., 2018). This particular form of brain plasticity that characterizes the birth process is coordinated by oxytocin molecules dispersed into the blood stream from the maternal posterior pituitary gland. The aforementioned polarity switch of GABA signaling is thought to protect certain fetal neurons from periods of transient hypoxia that accompanies early-life stress (Tyzio et al., 2006). This, together with the fact that oxytocin plays an active role in stress-related responses, suggest that oxytocin is reciprocally intertwined with cortisol activity, although the extent of this relationship is not fully understood (Leuner et al., 2012; Latt et al., 2018; Zinni et al., 2018). If endogenous oxytocin indirectly protects the fetal brain from hypoxic stress, what are the long-term implications of Pitocin administration on breathing behaviors? Breathing behavior originates from excitatory (i.e., depolarizing) and inhibitory (i.e., hyperpolarizing) cell networks within the medulla oblongata of the brainstem (Baertsch et al., 2019). Additional neuronal columns within the brainstem also contribute to breathing-related behaviors such as suckling, swallowing, chewing and gasping, integrated behaviors that must be precisely coordinated for successful early-feeding (Gross and Trapani-Hanasewych, 2017). Thus, future work will need to take a broader look at the mechanisms that may underlie breathing behavior, including the developmental consequences of exogenous oxytocin levels on excitatory and inhibitory gradients that control breathing phenomena.

6.3. Linking Pitocin administration to aggregation of human proteins

During normal pregnancy, additional hormones (e.g., CRF, GnRH) are secreted from maternal and fetal brains, the placenta, the myometrium and decidual tissue that contribute further to the programming and timing of spontaneous labor (Voltolini and Petraglia, 2014). One of these pregnancy-associated molecules is the Pregnancy Zone Protein (PZP) which increases substantially in maternal blood plasma throughout the fetal growth spurt (Ekelund and Laurell, 1994). PZP is a macromolecule synthesized in trophoblasts of the placenta closely related in sequence homology and structure to human α-2-macroglobulin (Devriendt et al., 1991), both of which act as protease-inhibitors in biological fluids (Chiabrando et al., 2002). PZP also stabilizes misfolded proteins, including the amyloid-β peptide which forms pathological plaques in Alzheimer's disease (AD) and preeclampsia, a pregnancy-specific disorder (Cheng et al., 2016; Cater et al., 2019). Of particular interest, high serum levels of PZP are detected in pre-symptomatic AD patients (Ijsselstijn et al., 2011), and immunolabeling of the placental protein is also observed in postmortem AD brains (Nijholt et al., 2015). Overall, these findings imply that human pregnancy leads to pervasive rewiring of

protein-protein interactions which allows the accumulation of misfolded proteins in healthy placentas and placentas of women with preeclampsia (Wyatt et al., 2016). Thus, the physiological role of PZP is to efficiently prevent the aggregation of full-length amyloid-β peptides into toxic amyloid fibrils (Cater et al., 2019). The dramatic rise of oxytocin during pregnancy may also play a role in buffering the fetus from protein damage experienced by the maternal body. Indeed, oxytocin signaling is implicated in stress reduction (see above) and perhaps the unique expression of this hormone *in utero* is to maintain protein homeostasis for a successful and unabated pregnancy. Based on the current evidence, it is conceivable that oxytocin signaling during sensitive periods of protein remodeling may protect the mother-fetal unit against deposition of misfolded proteins. If such protection exists, further research is likely to illuminate the importance of oxytocin-PZP interactions and could also reveal positive contributions of Pitocin administration on a small but growing subset of children worldwide.

6.4. Pitocin administration and cardiovascular function

The fact that Pitocin administration yields both negative and positive behavioral phenotypes in humans suggests that oxytocin signaling is subject to tissue-specificity, differences in receptor polymorphism and differences in drug metabolism (Kenkel et al., 2014; Gottlieb, 2016). An appropriate example of this dichotomy is the protective role oxytocin signaling exerts against atherosclerotic cardiovascular disease (Jankowski et al., 2016; Wang et al., 2019). Although this causal link is currently based on animal findings, it should be noted that structures regulating cardiac activity are densely populated with the oxytocin GPCR (Jankowski et al., 1998, 2010). Regardless, the possibility that oxytocin function might help in the management of both congenital and acquired heart disease has implications for medical therapy and drug development. In contrast, the occurrence of aortic dissection, often associated with pregnancy and childbirth, is ascribed to untoward oxytocin signaling as blockage of the oxytocin receptor attenuates aortic tearing in a mouse model of Marfan syndrome (Habashi et al., 2019). Marfan syndrome is a connective tissue disorder characterized by cardiovascular and musculoskeletal deficits derived from pathogenic variants of the fibrilin-1 gene (Fusco et al., 2019). The divergence of findings from rodent studies highlights the complex and diverse interactions oxytocin has with the genome, epigenome and proteome. Given the dual functions of oxytocin in certain physiological endpoints of health and disease, what are the implications of Pitocin administration for human offspring with congenital heart disease? Would Pitocin administration advance or retard acquired heart disease? From a broader perspective, how do past experiences of Pitocin exposure affect nascent physiological and cellular pathways leading to health improvement or disease susceptibility? Answers to these questions will define key biological and clinical features of how experiences sustained during early-life can linger into adulthood and beyond.

7. Conclusions

A growing body of evidence supports the theory that the judicious use of Pitocin has important clinical benefits for newborn babies and their mothers. The studies discussed in this manuscript suggest that administration of Pitocin to women undergoing labor may produce modest short-term effects on the well-being of their offspring. It remains to be seen, however, what the long-term consequences of Pitocin infusions are for the human adult. We hypothesize that the potential effects of Pitocin administration are likely driven by events in the periphery, which then impact nascent hypothalamic neurons to produce a wide-range of behavioral outcomes. The rather complex picture of oxytocin signaling pathways, including the cumulative activity of several cell-types, with their myriad interactions, evolutionary histories and environmental experiences make this obstetric topic a bewildering but important endeavor for future studies.

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