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ORIGINAL ARTICLE

The dynamic serotonin system of the maternal brain

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Abstract

Many pregnant and postpartum women worldwide suffer from high anxiety and/or depression, which can have detrimental effects on maternal and infant well-being. The first-line pharmacotherapies for prepartum and postpartum affective disorders continue to be the selective serotonin reuptake inhibitors (SSRIs), despite the lack of large well-controlled studies demonstrating their efficacy in reproducing women and the potential for fetal/neonatal exposure to the drugs. Prepartum or postpartum use of SSRIs or other drugs that modulate the brain's serotonin system is also troubling because very little is known about the typical, let alone the atypical, changes that occur in the female central serotonin system across reproduction. We do know from a handful of studies of women and female laboratory rodents that numerous aspects of the central serotonin system are naturally dynamic across reproduction and are also affected by pregnancy stress (a major predisposing factor for maternal psychopathology). Thus, it should not be assumed that the maternal central serotonin system being targeted by SSRIs is identical to non-parous females or males. More information about the normative and stress-derailed changes in the maternal central serotonin system is essential for understanding how serotonin is involved in the etiology of, and the best use of SSRIs for potentially treating, affective disorders in the pregnant and postpartum populations.

Keywords Dorsal raphe · Neuroplasticity · Postpartum anxiety · Postpartum depression · Serotonin · SSRI

Recent analyses indicate that at least 10–15% of the millions of pregnant and parturient women worldwide each year are faced with a depressive disorder and at least 8–10% suffer from an anxiety disorder (Fairbrother et al. 2016; Goodman et al. 2016; Le Strat et al. 2011; Reck et al. 2008). When one further considers the many pregnant and postpartum women with high, but subclinical, depressive and anxious symptoms, the number of affected women is extremely troubling. Mental health problems at any time of life are certainly a cause for concern, but heightened attention to them during this period of possibly increased susceptibility (see Davé et al. 2010; O'Hara et al. 1990; Britton, 2008) is especially important because there are few times in a woman's life when the stakes of having a depressive or anxiety disorder are as high. Indeed, a peripartum psychiatric admission is a greater mortality risk for women compared to almost all other causes, including heavy smoking (Appleby 1998; Chesney et al. 2014). Depression or anxiety during pregnancy and postpartum are also each associated with a host of other negative outcomes for mothers and their infants. At their extreme, maternal depression and anxiety contribute to infant neglect and abuse, but more commonly are associated with lower rates of breastfeeding, lack of maternal emotional and behavioral sensitivity to the infant, poor mother-infant bonding, negative infant temperament, altered infant neurodevelopment, and emotional and behavioral problems in the children when they are older (Drury et al. 2016; Field 2010; Glasheen et al. 2010; Stein et al. 2014). Because of a desperate need for increased attention to maternal affective disorders, the United States Preventive Services Task Force and the American College of Obstetricians and Gynecologists each recently recommended routine mental health screening for all pregnant and postpartum women (Committee on Obstetric Practice 2015; O'Connor et al. 2016).

The first-line pharmacotherapies for affective disorders in pregnant and postpartum women are the serotonin reuptake inhibitors (SSRIs). SSRIs are prescribed to ~2–8% of pregnant women and ~4% of early postpartum women in the United

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States; even higher usage can be found elsewhere (e.g., > 9% in the U.K.) (Alwan et al. 2011; Andrade et al. 2008; Charlton et al. 2015; Hanley and Mintzes 2014; Huybrechts et al. 2013; Lupattelli et al. 2014; Munk-Olsen et al., 2012). This is true despite concerns about placental and breastmilk transference of the drugs or their metabolites impacting fetal and neonatal development (Glover and Clinton 2016; Oberlander et al. 2009; Weisskopf et al. 2015), as well as the lack of large double-blind, placebo-controlled studies of SSRIs involving reproducing women (De Crescenzo et al. 2014; McDonagh et al. 2014; Molyneaux et al. 2015).

How SSRIs may alleviate depression and anxiety is unclear, but the mechanisms at least initially involve elevated central serotonergic signaling. Some supporting evidence for this includes that SSRIs have lower clinical efficacy in people with serotonin transporter gene (*SERT*) polymorphisms that yield low transcriptional activity (Ruhé et al. 2009; Serretti and Kato 2008), that some strains of SERT-knockout rodents show abnormally high depressive- and anxiety-like behaviors (Holmes et al. 2002; Kalueff et al., 2007; Lira et al. 2003; Olivier et al. 2008), and that SERT-knockout mice are resistant to SSRIs' antidepressant behavioral effects (Holmes et al. 2002). After elevating serotonergic activity, the downstream consequences of SSRIs on the brain include neuroplastic changes (e.g., cell birth and survival, cell death, synaptogenesis, dendrite morphology, and axonal outgrowth) within the hippocampus, cortex, and even back on the serotonin system itself that facilitate adaptation to stress (Haase and Brown 2015; Pittenger and Duman 2008). Eliminating the signaling of a major neurotrophic factor mediating many types of neuroplasticity, brain-derived neurotrophic factor (BDNF), by mutating its TrkB receptor gene in the hippocampus or midbrain dorsal raphe (DR; the source of most forebrain-projecting serotonin cells (Lowry et al. 2008) prevents SSRIs' positive effects on neuroplasticity and affective behaviors in laboratory rodents (Adachi et al. 2017; Horne et al. 2008; Li et al., 2008; Monteggia et al. 2004; Saarelainen et al. 2003).

Concern about the high rate of SSRI use by pregnant and postpartum women also comes from the fact that we know very little about how SSRIs may act uniquely on the pregnant and postpartum brain. Due to the physiological adaptations of reproduction that alter drug absorption, distribution, metabolism, and elimination (Anderson 2006; Pariente et al. 2016), SSRI doses are often increased for pregnant and early postpartum women in order to maintain drug blood levels and hopefully their clinical efficacy (Crescenzo et al. 2014; Hostetter et al. 2000; McDonagh et al. 2014; Molyneaux et al. 2015). However, this is based on insufficient empirical evidence. A small longitudinal study of 11 women found a late-pregnancy drop in plasma concentrations of the SSRI, citalopram, although most of the women did not require an increased dose to maintain euthymia (Heikkinen et al. 2002). Two other small longitudinal studies assessing women from pregnancy week 20 to 3 months postpartum also revealed increased SSRI drug clearance during pregnancy, but not in all of the women (Sit et al. 2008, 2010). Yet another small study found no significant differences across pregnancy in metabolism of the SSRI, sertraline, but noted very large individual differences among the women (Freeman et al. 2008). Such individual differences in SSRI metabolism are partly due to genotypic differences in drug-metabolizing cytochrome 450 liver enzymes, (Ververs et al. 2009) and are associated with women's continuance or discontinuance of their antidepressants (Berard et al. 2017). To further complicate things, a very recent analysis of blood samples from almost 300 pregnant women found that third-trimester drug concentrations were lower than baseline only for some SSRIs (paroxetine, citalopram), were higher than baseline for another SSRI (sertraline), and did not change for two others (escitalopram and fluoxetine) (Westin et al. 2017). In addition to this complex collection of results raising questions about the frequent practice of increasing SSRI doses for pregnant and early postpartum women, adjusting SSRI doses to maintain blood drug levels does not consider any distinctive effects that SSRIs may have on the central nervous system of reproductive women, and assumes that their brain serotonin system is identical to non-reproductive women. The handful of studies detailed immediately below demonstrates that this is not the case.

Pregnancy and the postpartum period involve some of the most dramatic neurobiological modifications that can occur in adulthood, and these modifications collectively facilitate a mother's ability to care for her young (Galea et al. 2014; Gammie et al. 2016; Kim et al. 2016; Leuner and Sabihi 2016). However, there has been little attention to how the brain's serotonin system is naturally affected by female reproduction, even though it is known to be sensitive to experimental manipulations of ovarian hormones in female rodents and monkeys (Bethea et al., 2002; Chavez et al. 2010; Donner and Handa 2009; Fink et al. 1996; Inagaki et al. 2010). A number of studies have reported that female reproduction normatively upregulates central serotonergic activity. Women in their second trimester of pregnancy or at term have higher cerebrospinal fluid serotonin metabolites compared to non-pregnant women (Spielman et al. 1985), and pregnant or postpartum women have higher plasma serotonin than do non-reproducing women (Sekiyama et al. 2013). Seemingly inconsistent with these results are other studies finding that late pregnancy and the early postpartum period are associated with relatively low serum levels of the serotonin precursor, tryptophan (Handley et al. 1980; Badawy 2014; Maes et al. 2002; Veen et al., 2016). Although reduced plasma tryptophan may be expected to reduce the capacity for brain serotonin synthesis (Fernstrom and Wurtman 1971), it is important to note that plasma trytophan alone does not dictate the brain's capacity to produce serotonin (Fernstrom and Wurtman 1972).

In laboratory rats, serotonin cell firing in the midbrain dorsal raphe is higher in pregnant and early postpartum females when compared to cycling females (Klink et al. 2002), and we have found that dorsal raphe levels of tryptophan hydroxylase 2 (TPH2; the rate-limiting enzyme for central serotonin synthesis) and serotonin metabolism (as indicated by the serotonin metabolite 5-hydroxyindoleacetic acid; 5HIAA) are higher in early postpartum rats compared to diestrus, nulliparous females (Harding and Lonstein 2016; Holschbach and Lonstein 2016). Early postpartum rats also have non-statistically significant, but considerably higher (> 30%), SERT in their dorsal raphe compared to non-maternal female rats (Harding and Lonstein 2016). On the other hand, a study using a small sample of postpartum day 10 laboratory mice found that these females had less serotonin immunoreactivity in their dorsal raphe compared to cycling females (Jury et al. 2015). We did not find this difference in dorsal raphe serotonin immunoreactivity in a large study of laboratory rats sacrificed as diestrous virgins or on postpartum days 8 or 19 (Holschbach and Lonstein 2016), though, perhaps suggesting species-specific effects of female reproduction on the midbrain serotonin system. At the serotonin receptor level, we recently found > 50% less excitatory serotonin 2C receptor mRNA expression in the postpartum rat dorsal raphe compared to females sacrificed during the estrus cycle or mid-pregnancy (Vitale et al. 2017). Because the serotonin 2C receptor is often found on inhibitory GABAergic cells in the dorsal raphe (Serrats et al., 2005), its reduced expression likely contributes to the elevated dorsal raphe serotonin cell excitability and output during late pregnancy and the early postpartum period (Boothman et al. 2006). Not only is the midbrain serotonin system affected by female reproduction, but frontocortical serotonin content and turnover rises across pregnancy and then falls postpartum in rats (Desan et al. 1988; Glaser et al. 1990), and serotonin turnover in two basal forebrain sites involved in maternal caregiving and anxiety (i.e., the medial preoptic area and bed nucleus of the stria terminalis) is higher in postpartum rats compared to diestrous virgin females (Lonstein et al. 2003; Smith et al. 2013).

These motherhood-induced neurochemical changes in the serotonin system are accompanied by neuroplastic changes. Contrary to early thinking that the adult mammalian brain is extremely limited in its neuroplasticity, remarkable alterations in brain cell birth, survival, differentiation, and death are now known to continue throughout the lifespan and particularly during times of hormone-induced neurobehavioral flux (Sisk et al. 2013). For instance, a number of research groups have shown in laboratory rodents and sheep that giving birth and interacting with young affect the proliferation of newborn cells in the subgranular zone (SGZ) of the hippocampus, as well as the survival of those cells after they migrate to the nearby granule cell layer (Leuner and Sabihi, 2016; Lévy et al. 2017; Pawluski and Galea 2007). The functional significance of motherhood-induced changes in hippocampal cell birth and survival are unknown, but they may partly underlie how the hippocampus is involved in the blunted hypothalamic-pituitary adrenal (HPA) axis response to stress during pregnancy and postpartum (Brunton et al. 2008). Female reproduction also affects the number of cells born in the subventricular zone (SVZ) that lines the walls of lateral ventricles, from which the cells migrate to the main olfactory bulb and contribute to the postpartum display of maternal caregiving behaviors (Corona et al. 2017; Furuta and Bridges 2005; Larsen and Grattan 2010; Shingo et al. 2003).

While the far majority of studies of adult brain cell proliferation and survival have focused on the SGZ/hippocampus and SVZ/main olfactory bulb, a number of other adult brain regions do contain newborn cells (Akbari et al. 2007; Lévy et al. 2017). We recently found that this includes the midbrain dorsal raphe. By using systemic injections of the thymidine analogue, bromodeoxyuridine (Brdu), to later identify mitotic cells in the dorsal raphe of different groups of adult nulliparous, pregnant, and postpartum rats, we found that Brdu-containing cells born during the early postpartum period were less likely to survive almost 2 weeks later into late lactation when compared to cells that were born during late pregnancy (Holschbach and Lonstein 2016). Cytogenesis in the adult dorsal raphe had not previously been reported in any animal, but it was not completely unexpected because the lining of the cerebral aqueduct lying just above the dorsal raphe is a highly proliferative niche generating midbrain cells during other developmental epochs (Arenas et al. 2015). The differences we found between pregnancy-born and postpartum-born dorsal raphe cells in their survival were paralleled by dorsal raphe immunoreactivity for the cell differentiation factor, NeuroD, and many of the surviving cells could in fact be phenotyped as young neurons (Holschbach and Lonstein 2016). The relatively low survival of cells born in the early postpartum dorsal raphe required that mothers interacted with pups, because removing the litter soon after parturition increased dams' newborn cell survival. Consistent with the ability of early litter removal to increase newborn cell survival in the maternal dorsal raphe, dams whose litters were removed at parturition also showed less programmed cell death (i.e., apoptosis) compared to dams that remained with their offspring (Holschbach and Lonstein 2016). It may seem surprising to some readers that we found that motherhood is associated with lower dorsal raphe newborn cell survival and higher cell death. Regressive events such as cell death and synaptic pruning are essential for refining and optimizing neural circuit function (Chechik et al. 1999; Fricker et al. 2018), and thus are surely relevant for neurobehavioral changes across the peripartum period and lactation (Pereira 2016). Whether the motherhood-related

neuroplasticity we found in the dorsal raphe is a cause, result, or unrelated to the motherhood-related serotonin changes there and elsewhere in the brain remains to be determined.

The studies discussed above reveal a number of normative neurochemical and cellular changes in the serotonin system across female reproduction, but we know almost nothing about how these normative changes may be derailed by stress, or if stress can produce completely novel effects on this system. The dorsal raphe and other serotonin cell groups are rich in the receptors for stress-related hormones such us glucocorticoids and corticotrophin releasing hormone (CRH), and receive direct neuronal input from CRH cells in the amygdala, bed nucleus of the stria terminalis, and paraventricular nucleus of the hypothalamus (Aaronson et al. 1988; Fox and Lowry 2013). This is relevant because pregnancy stress is strongly associated with prepartum and postpartum affective disorders in women (Britton 2008; Lancaster et al. 2010; Robertson et al. 2004; Soderquist et al. 2009) and stress produces these effects, in part, by interacting with serotonin (Bethea et al. 2013; Costas et al. 2010; Mehta et al. 2012; Mitchell et al. 2011; Pinheiro et al. 2013). Pregnancy stress can also increase later postpartum depression- and anxiety-like behaviors in laboratory rodents (Darnaudery et al. 2004; Haim et al. 2014; Hillerer et al. 2011; Leuner et al. 2014; O'Mahony et al. 2006; Smith et al. 2004; although see Pawluski et al. 2011, 2012a), but only two studies have examined if pregnancy stress alters any aspect of the maternal central serotonin system. These studies found that stressed postpartum dams had higher serotonin turnover in the cortex (Gemmel et al. 2016) and lower cortical and hippocampal serotonin 1A receptor expression (Szewczyk et al. 2014), compared to unstressed dams when the subjects' brains were assessed in late lactation. Relevant to SSRI's/serotonin's downstream effects on neurotrophic factors, pregnancy stress in rodents has also been found to reduce BDNF levels in the maternal hippocampus and cortex (Maghsoudi et al. 2014; Miao et al. 2018), as well as atrophy neuronal dendrites in the maternal hippocampus and nucleus accumbens (Haim et al. 2014; Pawluski et al. 2012b).

It is mostly unknown if the neurochemical and cellular changes in the serotonin system across reproduction described above affect mothers' physiological or behavioral responses to SSRIs. It was recently found that the SSRI fluoxetine decreases body weight, lowers circulating cortisol, and increases neurogenesis in the hippocampus of nulliparous rats but not in postpartum mothers (Workman et al. 2016). On the other hand, only in mothers did fluoxetine interact with cortisol to reduce circulating estradiol (Workman et al. 2016). The parity difference in fluoxetine's effect on cortisol is particularly interesting given the association between hypothalamic-pituitary-adrenal axis dysfunction and some types of depression in nonparous humans (Stetler and Miller 2011). Studies in mice have revealed parity differences in the behavioral responses to an SSRI, with citalopram decreasing the latency for postpartum mothers but not nulliparous females to become immobile in a forced-swim test - a common paradigm used to assess depressive-like behavioral dispair in laboratory rodents (Jury et al. 2015). In rats, though, the high immobility in the forced-swim test shown by both mothers and nullipare treated with corticosterone can be reversed by fluoxetine (Workman et al. 2016).

In sum, SSRI use is widespread during pregnancy and the early postpartum period, and there is no reason to expect that this will change anytime soon (Hanley and Mintzes 2014). There are relatively few studies of the normative and stress-induced changes in the central serotonin system across female reproduction in either humans or laboratory rodents, but this information is critical for understanding how serotonin and its downstream effects on neuroplasticity and other brain processes contribute to the etiology of postpartum depression and anxiety. Understanding the unique aspects of the maternal serotonin system is also essential for optimizing the dose and timing of SSRIs, or any other pharmacotherapies affecting the brain's serotonin system, when they are to be used as potential treatments for prepartum and postpartum affective disorders.

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Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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