THEMATIC REVIEW

SULFATION PATHWAYS

The steroid sulfate axis and its relationship to maternal behaviour and mental health

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Abstract

Steroid hormones can exist in functionally dissociable sulfated and non-sulfated (free) forms and can exert profound effects on numerous aspects of mammalian physiology; the ratio of free-to-sulfated steroids is governed by the antagonistic actions of steroid sulfatase (STS) and sulfotransferase (SULT) enzymes. Here, I examine evidence from human and animal model studies, which suggests that STS and its major substrate (dehydroepiandrosterone sulfate, DHEAS) and product (DHEA) can influence brain function, behaviour and mental health, before summarising how the activity of this axis varies throughout mammalian pregnancy and the postpartum period. I then consider how the steroid sulfate axis might impact upon normal maternal behaviour and how its dysfunction might contribute towards risk of postpartum psychiatric illness. Understanding the biological substrates underlying normal and abnormal maternal behaviour will be important for maximising the wellbeing of new mothers and their offspring.

Key Words
- dehydroepiandrosterone sulfate
- postpartum depression
- postpartum psychosis
- steroid sulfatase
- sulfotransferase

An introduction to the steroid sulfate axis

Steroid hormones are synthesised within a number of endocrine body tissues (notably the adrenal gland, gonadal, breast, adipose and liver tissue in primates), and, as well as being utilised locally, may subsequently transported elsewhere to elicit widespread physiological effects. The hydrophobicity of free steroids limits their ability to be transported within aqueous media; hence, transport of these compounds is facilitated by the addition of negatively charged sulfate groups through esterification by the steroid sulfotransferase (SULT) enzymes SULT1E1, SULT2A1 or SULT2B1b, or, to a lesser extent, by SULT1A1 or SULT2B1a (Salman et al. 2011, Mueller et al. 2015). In addition to increasing the solubility of steroids, sulfation processes also increase their stability: circulating concentrations of sulfated steroids are typically substantially higher than circulating concentrations of their free steroid counterparts, and the former may act as ‘reservoirs’ for the peripheral formation of bioactive hormones (Mueller et al. 2015). Many common steroids can be sulfated including cholesterol, pregnenolone, estrone and dehydroepiandrosterone (DHEA) (Mueller et al. 2015).

Upon influx into cells in target tissues via organic anion transporter proteins, sulfated steroids are typically
desulfated by hydrolysis to their unconjugated forms, which are generally considered to be more biologically active and which can act as precursors for a variety of androgens and estrogens. Whilst multiple sulfotransferases can facilitate sulfation according to tissue type, there is just one ubiquitous enzyme that cleaves sulfate groups from steroids: steroid sulfatase (STS, formerly known as arylsulfatase C). In the interests of clarity and brevity, in this review, I focus upon the physiological roles of STS and dehydroepiandrosterone (DHEA), whose sulfated form (DHEAS) is the most abundant circulating steroid in humans (Neunzig & Bernhardt 2014).

Steroid sulfatase: its regulation, expression and function

Steroid sulfatase is encoded by the X-linked STS gene (Xp22.3). As the human STS gene escapes X-inactivation (Shapiro et al. 1979), and as its Y-linked parologue is pseudogenic (Yen et al. 1988), expression of STS is 1- to 2-fold higher in female than male tissues (including brain) during development and into adulthood, although whether this expression difference translates to significantly greater enzyme activity in female tissues is debatable (Cuevas-Covarrubias et al. 1993, Miranda-Duarte et al. 1999, Ugele & Regemann 2000, Nakamura et al. 2003, Steckelbroeck et al. 2004, Kriz et al. 2008, HE O’Brien et al. manuscript in preparation); nevertheless, the possibility certainly exists that the physiological consequences of STS activity modulation could feasibly be more profound in women than in men. STS is expressed in a number of tissues many of which are involved in reproductive function, including the placenta (highest expression), brain, ovary, mammary gland, testis, adipose tissue, thyroid gland and skin (Salido et al. 1990, Miki et al. 2002, Steckelbroeck et al. 2004, Stergiakouli et al. 2011, https://www.ncbi.nlm.nih.gov/unigene accessed 12th September 2017).

At the cellular level, the STS protein is largely located in the endoplasmic reticulum of the cell where it functions as a glycosylated homodimer; the catalytic activity of STS is dependent upon the presence of sulfatase-modifying factors (SUMFs) (Mueller et al. 2015). STS activity appears to be increased in response to stress/inflammation in various tissues with the gene being a target of NF-KB; the resultant free steroid products, notably estrogens, may act as inflammation suppressors (Dias & Selcer 2016, Jiang et al. 2016). STS has long been recognised as a therapeutic target in hormone-dependent cancers, and a number of effective and specific STS inhibitors have been developed, which reduce the pool of androgens and estrogens in the vicinity of the cancer and which have potential clinical benefits (Purohit & Foster 2012).

The steroid sulfate axis: its influence on brain function and behaviour

Seminal work in rodents suggested that, in mammals, some steroids (and hence their sulfate conjugates) such as DHEA(S) could be synthesised de novo in the brain and may be regarded as neurosteroids (Corpechot et al. 1981). Subsequent work has shown that, whilst DHEA biosynthesis within the brain is possible, a second route by which DHEA appears in the brain in rodents (and feasibly humans too) is through the uptake, and subsequent rapid desulfation, of circulating DHEAS by organic ion transporters and STS, respectively, in the capillaries of the blood–brain barrier (Nicolas & Fry 2007, Qaiser et al. 2017). Whilst the expression patterns of STS in the human blood–brain barrier are yet to be systematically assessed, in the developing human brain, STS is highly expressed throughout the thalamus with lower expression also seen in the olfactory epithelium, the cerebral cortex, the basal ganglia, the hypothalamus and pituitary gland, the choroid plexus and the cerebellar neuroepithelium (Stergiakouli et al. 2011); in adulthood, high levels of STS expression and associated enzyme activity persist in these regions (Perumal et al. 1973, Steckelbroeck et al. 2004, Kriz et al. 2008). Although STS activity in the brain is likely to have important and widespread developmental and ongoing effects (see later), sulfatase activity in this tissue is apparently dominated by sulfotransferase activity, and, in support of this idea, levels of sulfated steroids in the human brain (including those of DHEAS) may be relatively high (Maninger et al. 2009, Mueller et al. 2015).

At the molecular level, free and sulfated steroid hormones can modulate receptors influencing acute neuronal inhibition and excitation, as well as neurodevelopmental processes. For example, both DHEAS and pregnenolone sulfate act as antagonists at GABA<sub>₄</sub> receptors, as agonists at σ receptors, and as positive modulators at N-methyl-D-aspartic acid (NMDA) receptors (Reed et al. 2005, Qaiser et al. 2017). Importantly, the sulfated and unconjugated steroids may have differential effects and potencies e.g. DHEA has been reported to act as a weaker GABA<sub>₄</sub> antagonist than DHEAS (Reed et al. 2005, Maninger et al. 2009). In addition to relatively weak agonistic effects at the androgen and oestrogen receptors, DHEA and DHEAS may bind to, and activate, neurotrophin TrkA and p75<sup>NTR</sup> receptors to attenuate neuronal apoptosis.
and hence influence neurodevelopment (Lazaridis et al. 2011).

Insights into the behavioural and brain processes that are mediated by STS and DHEA(S), potentially via the aforementioned molecular mechanisms, can be obtained by examining phenotypes in individuals in which (a) the STS gene is rendered non-functional (by natural or experimental means), (b) the STS enzyme is acutely inhibited by a selective drug or c) DHEA(S) has been administered. Less convincingly, it is possible to investigate the extent to which (peripheral) levels of DHEA(S) correlate with brain/behavioural phenotypes of interest, and hence, the extent to which changes in the former may cause the latter.

In humans, STS deficiency (arising from partial or complete deletion of the gene, or inactivating point mutations within it) results in the rare dermatological condition X-linked ichthyosis (XLI) (Fernandes et al. 2010). XLI chiefly affects males and is associated with an elevated DHEAS/DHEA serum ratio, especially pre-pubertally (Idkowiack et al. 2016). Whilst there is currently little published literature on brain structure/function and biochemistry in individuals with XLI (Trent & Davies 2013), there is an emerging literature suggesting that boys with the condition may be at increased risk of developmental disorders such as autism spectrum conditions (ASCs), attention deficit hyperactivity disorder (ADHD) and early-onset psychotic disorders (Kent et al. 2008, Chatterjee et al. 2016, Malik et al. 2017) whilst men with the condition may be at increased risk of both developmental and mood (unipolar depression and bipolar) disorders (Chatterjee et al. 2016). There is also some evidence that genetic variation within STS is associated with measures of attention in both clinical (ADHD) (Brookes et al. 2010, Stergiakouli et al. 2011, Wang et al. 2017) and healthy (Humby et al. 2017) populations. These behavioural findings are consistent with the high expression of STS in brain regions involved in integrating and acting upon sensory information and executive function.

Recapitulating the clinical findings in XLI, mice in which the Sts gene is deleted (or in which the STS enzyme is inhibited) show significantly reduced levels of serum DHEA and associated impairments in attention, altered response inhibition, hyperactivity, heightened emotional reactivity and aggression and increased levels of behavioural perseveration (Davies et al. 2009, 2014, Trent et al. 2012b, 2013). Animal models allow the neurochemistry underlying behavioural abnormalities to be studied. Sts deletion in mice is associated with higher serotonin levels in the striatum and hippocampus (together with elevated hippocampal expression of the serotonin receptor 2c (Htr2c) gene), and reduced striatal noradrenaline turnover; the extent of serotonergic perturbation in Sts-deficient mice seems to correlate with the severity of some behavioural phenotypes (Trent et al. 2012a). Pharmacological studies in rats in which the STS enzyme was acutely inhibited have revealed changes in hippocampal acetylcholinergic release together with parallel changes in memory function (Rhodes et al. 1997, Babalola et al. 2012, Yue et al. 2016).

Experimental and correlational studies in animal models and human populations have linked altered DHEA(S) levels to a diverse and important range of behavioural phenotypes including: sexual function (Peixoto et al. 2017), aggression (Nicolas et al. 2001, Soma et al. 2015), locomotor activity (Strous et al. 2001, Trent et al. 2012b, 2013) and numerous aspects of mood and cognition (including attention) (Rhodes et al. 1996, Davies et al. 2009, Pluchino et al. 2015, Starka et al. 2015).

The data presented above establish that STS (and its dysfunction) can impact extensively upon normal brain function via multiple neural and neurochemical pathways; this action may be direct (i.e. within the brain itself), or, alternatively, may result from extra-brain STS activity impacting upon the production and action of circulating levels of sulfated and free steroids including DHEA(S).

Changes in the steroid sulfate axis throughout mammalian pregnancy and the postpartum period

Throughout the childbearing process, women experience considerable hormonal fluctuations, including with regard to the steroid sulfate axis (Tal et al. 2000). However, longitudinal studies in which the levels, and sulfation status, of multiple hormones are measured across pregnancy and the postpartum period are scarce. Due to ethical and practical issues, most information in humans comes from analysis of peripheral tissues (blood, serum/plasma, saliva and rarely cerebrospinal fluid) and therefore its relevance to the hormonal milieu experienced directly by the brain is questionable. Moreover, peripherally detected maternal hormone levels may be influenced by multiple variable factors including: breastfeeding, stress exposure, use of recreational and therapeutic drugs, parity, maternal age and diet and gender/number/size of the foetus(es), and understanding how unstable hormone levels relate to specific physiological phenotypes is therefore challenging. Whilst the use of neurobiologically amenable mammalian animal models in which experimental variables can be controlled may circumvent these issues to some extent in...
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in vivo systems, such models differ from humans in terms of both circulating hormone levels and reproductive traits such as number of offspring per pregnancy or the extent and duration of postnatal maternal care; hence, extrapolating from models to man (or woman) should be done with caution.

In humans, from around nine weeks of pregnancy, a key role of the steroid sulfate axis is to generate precursors for the production of estrogens to be secreted into the maternal and fetal bloodstreams. Initially, sulfated C-19 steroids including DHEAS and 16α-OH-DHEAS produced by the maternal and fetal adrenal glands and fetal liver must undergo hydrolysis in the STS-rich syncytiotrophoblast of the placenta (Salido et al. 1990) before conversion by a series of enzymatic reactions to estrogens including estrone, estriol and estradiol; estrone, but not estradiol, is subsequently sulfated in the mother (Geyer et al. 2017).

As healthy pregnancies progress, there is a consistently observed decrease in maternal DHEAS serum levels from non-pregnancy levels (apparently independent of fetal gender), perhaps as DHEAS is increasingly utilised for oestrogen synthesis in the developing placenta; after parturition, maternal serum DHEAS levels rapidly rebound to pre-pregnancy levels (Tagawa et al. 2004, Soldin et al. 2005, Kuijper et al. 2013, Farrar et al. 2014). The data regarding systemic maternal DHEA levels throughout pregnancy and the postpartum period are less consistent. Some studies have demonstrated elevated serum/plasma DHEA levels during early-mid pregnancy, with a subsequent gradual decline up to one year postpartum (Nieschlag et al. 1974, Buckwalter et al. 1999, Tagawa et al. 2004); given DHEA’s immunosuppressive effects and an increase in maternal cytokine markers after childbirth, this pattern of effects has been postulated to provide maximum protection for the incipient foetus from maternal immune surveillance (Tagawa et al. 2004). Other studies have suggested that peripheral DHEA levels are relatively unaffected by pregnancy and parturition (Buster et al. 1979, Soldin et al. 2005) or even that they increase across pregnancy and towards parturition in peripheral tissues (saliva or plasma) (Bird et al. 1980, Hampson et al. 2013). If DHEAS levels do fluctuate as outlined above during pregnancy/postpartum period, and DHEA levels remain in a comparatively steady state, then the DHEA/DHEAS ratio would be expected to be high during pregnancy and low during the postpartum period relative to values in non-pregnancy; in healthy populations where this ratio has been assessed longitudinally, this pattern of effects is indeed observed (Hill et al. 2002, Tagawa et al. 2004).

Presumably the above changes in DHEA/DHEAS ratio over the course of pregnancy and the postpartum period are related to the relative abundance and/or activity of the STS and sulfotransferase enzymes in cells contributing towards the hormonal milieu of the periphery. A main contributor to this ratio is the syncytiotrophoblast cells of the placenta, and expulsion of the STS-rich placenta after birth likely explains the rapid restoration of circulating maternal DHEAS levels. However, other tissues may also contribute; in healthy women, STS activity in leukocytes has been reported to be greater in third trimester pregnant women than in first trimester pregnant, or non-pregnant, women (Miyakawa et al. 1994), a finding consistent with the observed high DHEA/DHEAS ratio during late pregnancy. To the best of my knowledge, there has not yet been any systematic analysis of peripheral (leukocyte) STS activity throughout the postpartum period in humans.

Peripheral levels of sulfated and free steroids cannot provide reliable information on the activity of steroid sulfatase in the brain, and direct measurement of brain STS activity throughout pregnancy and the postpartum period in humans is currently unachievable. However, animal models, such as rodents, might provide some insights into human physiology (bearing in mind the caveats discussed earlier with respect to cross-species extrapolation). Mortaud et al. (1996) showed that, in whole female mouse brain, STS protein levels were more than twofold higher in the lactating (postpartum) state relative to the pregnant (stage not specified) or non-pregnant state; whether this increase in protein level corresponded to an increase in enzyme activity in this state, or with brain DHEAS levels, was not assessed. Conversely, in rats, neither STS brain activity nor sulfotransferase liver activity appears to be affected by pregnancy or parturition although only cortical (as opposed to whole) brain tissue was analysed (Maayan et al. 2004a). Interestingly, data on STS activity in rat leukocytes partially resemble those seen in humans, in that activity is significantly higher in late-pregnancy animals (18 days post conception) than in non-pregnant animals, and becomes even more pronounced 24h after giving birth (Maayan et al. 2004a). In rat serum and brain cortex, the DHEA/DHEAS ratio is significantly, and equivalently, elevated in late pregnancy and early postpartum animals compared to non-pregnant control females (Maayan et al. 2004a).

In summary, the sparse human and rodent data presented above are reconcilable with the proposal that in non-cortical regions of the mammalian brain, and in certain cells of the immune system, STS levels/activity increase over the course of pregnancy before peaking.
during late pregnancy and into the early postpartum period.

**A possible role for the steroid sulfate axis in normal maternal behaviour**

Androgen-related metabolic pathways, including the STS/DHEA(S) axis, are known to modulate physiological processes associated with parturition (Makieva et al. 2014). Given the previously described role of the STS axis in brain and behavioural function, its increased activity in the perinatal period may be related to, and potentially be causal for, the emergence of maternal behaviours designed to nourish and protect their offspring. These behaviours, many of which are highly conserved across mammalian species, include nest-building, huddling, nursing and social interaction with the offspring mediated by olfactory, visual, auditory and somatosensory cues, altered (generally decreased) levels of anxiety with increased exploratory behaviour and aggression directed towards threatening predators/society members but not offspring (Bridges 2015, Lonstein et al. 2015). In rodents, and probably also in humans, the quality and intensity of expressed maternal behaviours is related to maternal cognitive (executive) function, particularly in the domains of offspring-related learning and memory processes, attention to relevant care cues, behavioural flexibility and impulse regulation; interestingly, in rats, reduced maternal behaviour is associated with impaired performance on attentional set-shifting and startle/prepulse inhibition tasks, whilst increased maternal care (pup-licking) is related to reduced motor impulsivity (Lonstein et al. 2015). In non-primate species, and in primates to a lesser extent, these behaviours are driven by hormonal mechanisms acting via a multitude of brain regions and neurochemical systems, including the prefrontal cortex, the amygdala, the cholinergic basal forebrain activating system and the GABAergic and serotonergic systems (Bridges 2015, Lonstein et al. 2015). The fact that manipulation of the STS axis in males affects many of the cognitive/behavioural phenotypes and neurobiological systems listed earlier (notably attention, social interaction, emotional reactivity, aggression, memory, behavioural flexibility and motor impulsivity (Mortaud et al. 1996, Rhodes et al. 1997, Kent et al. 2008, Davies et al. 2009, 2014, Trent et al. 2012a,b, 2013, Chatterjee et al. 2016)) supports the argument that the STS axis influences neural processes pertinent to maternal care efficacy in females. To explicitly test the idea that the STS axis influences maternal perinatal behaviour, studies will need to be undertaken in non-pregnant (control), pregnant and postpartum female animal models and human subjects in whom STS activity is compromised or in whom DHEA(S) levels are systematically varied and assayed.

The only currently-available Sts-deficient genetic rodent models are chromosomally mutant mice that are necessarily male (Trent et al. 2012b), but new gene-editing technology should hopefully allow the generation of Sts-deficient female rodents (Baud & Flint 2017). The expectation that such genetically modified female rodents may exhibit STS-dependent abnormal maternal behaviours has been raised by a recent pharmacological study in our laboratory. Briefly, we showed that acute inhibition of STS in new mouse mothers resulted in anxiety-related phenotypes (a reduced startle response and increased rearing and exploratory drive on the elevated plus maze), but no gross abnormalities in nest maintenance or in mother–pup interactions (Humby et al. 2016). At this stage, we cannot discount the fact that there were subtle, undetectable, irregularities in dam–pup interactions, especially in light of the fact that inhibitor-treated mothers exhibit substantial dysregulation of olfactory-related gene expression in the brain (Davies, unpublished results). Furthermore, as we did not examine the behavioural effects of acute STS inhibition in female mice with other physiological statuses (virgin, non-virgin but non-pregnant and pregnant), we cannot definitively say that the behavioural effects mediated by the STS axis are specific to the postpartum period; this extended analysis is ongoing. We are currently undertaking a parallel systematic study of behaviour, including perinatal behaviour, in STS-deficient women with a view to determining which, if any, psychological processes are affected by their genetic mutation.

Additional evidence that DHEA(S) participate in normal perinatal maternal behaviours in humans may be obtained by showing behavioural effects elicited by administration to new mothers or by identifying significant correlations between systemic DHEA(S) levels and behavioural/cognitive measures in healthy (or general population) postpartum mothers. Although DHEAS administration has been performed in postpartum women (e.g. Aisaka et al. 1984), there is no reliable published data available regarding parallel behavioural changes. In healthy women selected from the general population, there is some evidence for an association between higher serum DHEA levels, enhanced mood and aspects of better cognitive performance during late pregnancy (~20 days prior to delivery) and the postpartum period (~26 days...
after delivery) (Buckwarter et al. 1999), although no similar relationship seems to exist for DHEAS levels (Farrar et al. 2014).

Postpartum psychiatric disorders

A significant proportion of women experience mental health issues manifesting in late pregnancy and/or in the postpartum period. These can range from relatively common and comparatively mild conditions, which do not require medical intervention (so-called ‘baby blues’) to rarer, more severe, persistent and disabling disorders, which require urgent medical care; the latter category of disorders includes postpartum depression, obsessive-compulsive disorder and anxiety disorders (Sharma & Sommerdyk 2015, Stewart & Vigod 2016, Pawluski et al. 2017). If the steroid sulfate axis is indeed a major player in maternal brain and behavioural function in late pregnancy and the postpartum period as has been argued above, then, logically, its dysfunction might reasonably be considered a risk factor for vulnerability to maternal mental health conditions in this period. In the following section, I discuss the nature and aetiology of one extremely severe and poorly understood psychiatric disorder associated with childbirth, postpartum (or puerperal) psychosis, and consider evidence implicating steroid sulfate axis abnormalities in its pathogenesis.

The nature and aetiology of postpartum psychosis

Postpartum psychosis (PP) is estimated to affect 1–2 in every 1000 new mothers (VanderKruik et al. 2017). Symptoms associated with the condition include hallucinations, delusions (often related to the newborn child), cognitive disorganisation, anxiety and mood abnormalities, and these tend to present within the first two weeks (and frequently within the first few days) of childbirth; PP symptoms can impact massively upon normal mother–child bonding and family life, and affected mothers are at elevated risk of committing suicide or infanticide (Bergink et al. 2016). Whilst there is thought to be a considerable biological component to disorder vulnerability, the exact nature and contribution of underlying biological risk factors is currently obscure (Jones et al. 2014, Bergink et al. 2016). Understanding these may help to develop better predictive biomarkers for the condition, as well as more effective and safer treatment options (Davies 2017). Epidemiological data have suggested considerable overlap with bipolar disorder, autoimmune thyroid conditions and pre-eclampsia (Jones et al. 2014, Bergink et al. 2016); other studies have implicated an abnormal (over-active) immune system (Bergink et al. 2013, Kumar et al. 2017), autoimmune anti-NMDA receptor encephalitis (Bergink et al. 2015) and serotonergic system dysfunction (Kumar et al. 2007, Davies 2017) in risk. A genetic linkage study in bipolar PP implicated significant and suggestive loci at 16p13 and 8q24, respectively (Jones et al. 2007), but, to date, findings from small-scale (and therefore underpowered) candidate gene and genome-wide association studies have been unconvincing or non-significant, and none have yet implicated X-linked genetic risk variants.

Steroid sulfate axis dysfunction and PP risk

There are several lines of basic and clinical evidence suggesting that abnormalities with the steroid sulfate axis (and most likely STS deficiency Davies 2012) may influence PP risk: (a) the axis appears to exert disproportionately large effects in the late pregnancy/early postpartum period, so any disruption to it may impact relatively specifically on this timepoint, (b) estrogens are generally thought to be protective against psychosis (Reicher-Rossler 2017) and STS deficiency, in women, as in men (Lykkesfeldt et al. 1985), is expected to result in lower levels of circulating estrogens as a consequence of reduced levels of DHEA precursors, (c) genetic deletions encompassing STS have been associated with psychotic disorders (paranoid and early-onset schizophrenia) in case studies (Milunsky et al. 1999, Malik et al. 2017), (d) STS brain expression is high in regions previously implicated in psychotic disorders (Fusar-Poli et al. 2011, Dietsch et al. 2017), (e) the neurochemical abnormalities associated with psychosis and remediable by antipsychotic treatment overlap considerably with those influenced by STS and DHEA(S) i.e. of the serotonergic system (notably the 5-HT2C receptor) (Meltzer et al. 2012, Selvaraj et al. 2014), the hippocampal cholinergic system (Olincy & Freedman 2012, Carruthers et al. 2015), the GABA(A) system (Egerton et al. 2017) and of NMDA receptor signalling (notably in the thalamus) (Vukadinovic 2014, Harrison 2015), (f) STS-deficient humans and mice exhibit a range of PP-relevant phenotypes including inattention and emotional instability, whilst genetic variants within STS in man are associated with cognitive disorganisation (see above), (g) STS is highly expressed in the hypothalamus, pituitary gland and the thyroid gland (Stergiakouli et al. 2011) and its absence in these tissues could potentially explain high rates of hypothalamus–pituitary–thyroid axis dysfunction and autoimmune thyroid dysfunction.
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in PP, (h) abnormal placental and whole blood STS expression is associated with pre-eclampsia (Gratton et al. 2016), (i) levels of salivary DHEAS during late pregnancy and in the early postpartum period (10 days after birth) positively correlate with measures of anxiety, phobia, paranoia and psychoticism in previously healthy women, with highest DHEAS levels (consistent with impaired or absent STS activity) being associated with significant psychiatric distress (Marrs et al. 2009, 2010), (j) lithium, an established effective treatment for mania in bipolar disorder and PP, enhances the serum DHEA/DHEAS ratio in rats consistent with a stimulatory effect on STS, whilst reducing both brain and serum levels of DHEAS (Maayan et al. 2004b), (k) pathologically reduced levels of immunosuppressive DHEA in the postpartum period as a consequence of STS deficiency may feasibly contribute towards the immune hyperactivation seen in PP and (l) STS and the HTR2C (5-HT2C) gene lie under candidate quantitative trait loci linkage peaks in a porcine model of PP (Quilter et al. 2007). Finally, the prevalence of STS deficiency i.e. heterozygosity or homozygosity for null mutations in women is estimated to be ~1 in 950 individuals (based upon the general population frequency of STS deficiency in males (Langlois et al. 2009, Craig et al. 2010) and de novo vs inherited mutation rates (Cuevas-Covarrubias et al. 1999)); this rate is consistent with it being a risk factor for PP, although clearly, as for most mood and psychotic disorders, multiple interacting genetic and environmental risk factors are likely to influence overall PP vulnerability.

Future analyses, in STS-deficient women or in STS-deficient female rodents, are likely to provide evidence for or against the hypothesis that this molecular perturbation increases PP risk, although such studies will likely be limited by available sample size, by the infrequency of the condition and by cross-species extrapolation issues. Further studies in healthy women in late pregnancy and the postpartum period, which will be less constrained by sample size, might examine if, and how, peripheral STS activity (in addition to DHEA(S) levels) correlate with dimensional behavioural measures related to PP (e.g. psychoticism). Alternative complementary work in clinical PP populations might investigate: (a) variability within the STS gene (where rates of causal polymorphisms/mutations might be expected to differ from control women), (b) STS activity in accessible tissues such as leukocytes (lower activity anticipated in women affected by PP than in controls) or (c) peripheral baseline and stress-evoked levels of DHEA(S) (higher DHEAS/DHEA ratios expected in affected women vs control subjects).

Our mouse studies have provided preliminary evidence somewhat supportive of the notion of STS deficiency as a risk factor for PP. Briefly, we found that the behavioural phenotypes elicited by STS inhibition in new mothers could be partially reversed by administration of the clinically efficacious antipsychotic drug ziprasidone, thus indicating their potential relevance to PP (Humby et al. 2016). Additionally, and intriguingly, STS-inhibited mice demonstrated abnormal gene expression within a small region of chromosome 15 (equivalent to the 8q24 candidate genomic region implicated by linkage in PP), which could also be normalised by ziprasidone administration, providing further support for the model’s face and predictive validity and thus its utility for understanding the mechanistic basis of PP risk (Humby et al. 2016).

Steroid sulfate axis dysfunction in other postpartum psychiatric disorders

PP is an umbrella term covering a wide variety of behavioural and psychiatric symptoms, in addition to psychosis, that present shortly after childbirth. Many of these symptoms (which can include depressive and manic episodes, anxiety and obsessive-compulsive tendencies) may also be seen, to varying extents, in cases of other differentially defined postpartum psychiatric conditions such as postpartum depression and could be underpinned by common biological processes. Much of the logic implicating steroid sulfate axis dysfunction in general, and STS deficiency in particular, in PP pathophysiology may be equally applied to these alternative disorders, especially considering that their occurrence may, in part, be due to abnormalities in physiological and neurochemical systems affected by this axis i.e. steroid hormone levels, the hypothalamic–pituitary–adrenal axis, the thyroid system, markers of inflammation and the GABAergic, noradrenergic and serotonergic systems (Speisman et al. 2011, Skalkidou et al. 2012, Pawluski et al. 2017). The observed effects of STS deficiency on mood modulation (Chatterjee et al. 2016), behavioural (in) flexibility (Trent et al. 2013) and anxiety-related processes (Trent et al. 2012b, Chatterjee et al. 2016) implicate it as a candidate risk factor in postpartum depression, OCD and anxiety, respectively. The steroid sulfate axis could also feasibly mediate the effects of environmental factors (e.g. stressors such as childhood maltreatment) on mothers’ vulnerability to a range of postpartum psychiatric illnesses, and potentially even on their infants health (Sexton et al. 2015, Schury et al. 2017). Finally, the increased rate of
obstetric complications (notably delayed or prolonged labour) in STS-deficient women (Fernandes et al. 2010) may predispose them to postpartum psychopathology (Skalkidou et al. 2012)

Evidence examining rates of these various postpartum psychiatric conditions and associated behavioural and physiological markers remains to be collected in STS-deficient individuals and animal models; conversely, rates of STS deficiency remain to be determined in patients ascertained on the basis of having been diagnosed with such postpartum conditions. However, there are some limited existing data, consistent with the STS deficiency risk hypothesis, suggesting that circulating maternal DHEA plasma levels may be abnormally low prior to, and during the onset of, postpartum depression (Gelman et al. 2015), and that DHEA supplementation can benefit mood in depressed individuals (although consistent therapeutic benefits of this intervention in the postpartum period have yet to demonstrated) (Soares & Phillips 2006, Peixoto et al. 2014).

**Conclusions and future work**

In this article, I have discussed the mounting evidence (admittedly mainly obtained in male test subjects to date) that STS, and the reactions it catalyses, have important roles in a wide variety of important brain and behavioural functions. As the activity of the STS axis fluctuates across numerous tissues (including brain) during pregnancy, and into the postpartum period, it is conceivable that this axis bears upon normal maternal behavioural phenotypes and its influence in this respect remains to be tested using genetic and pharmacological approaches in clinical and model populations. In particular, gene expression changes elicited by manipulations of the steroid sulfate axis may be compared against those seen in the healthy postpartum maternal brain (Gammie et al. 2016). It also follows that, potentially, STS axis dysfunction may be associated with postpartum psychiatric conditions, and there is some circumstantial evidence, notably in PP, that this may be the case. Genetic and endocrine analyses in women previously affected by, or at high of developing, postpartum psychiatric conditions should be able to experimentally test this hypothesis.

Of course, whilst I have focussed upon the possible impact of STS and DHEA(S) on maternal behaviour here, it is naïve to think that these molecules act in isolation to affect this phenotype. As such, future studies should aim to supplement the currently available, very limited, data relating to the brain and peripheral expression and activity of enzymes and compounds involved in DHEA(S) biosynthesis and metabolism (notably the SULTs and SUMFs) across pregnancy and the postpartum period in healthy women, women affected by postpartum psychiatric illness, and relevant mammalian animal models, with a view to understanding how these components interact to generate healthy or abnormal behaviours. Work in model systems in particular may highlight molecules and pathways that mediate the behavioural effects of the steroid sulfate axis, and which could theoretically comprise novel therapeutic targets. For example, our nascent mouse work has implicated the CCN family of proteins as potentially druggable targets in cases of PP (Davies 2017). Pharmacological or genetic targeting of such mediators might result in lower levels of side effects compared to the systemic administration of compounds such as DHEA or estrogens, which have androgenic/oestrogenic potential and which elicit widespread effects on multiple physiological systems (Gentile 2005, Rutkowski et al. 2014).

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