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

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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 be 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 paralogue 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- κ B; 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_A 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_A 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^{NTR} 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

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 16 α -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 DHEA(S) 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 24 h 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) (Buckwalter *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 precursor, (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, Dietsche *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-HT_{2C} 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

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-HT_{2C}) 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 be 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).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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References

- Aisaka K, Mori H, Ogawa T & Kigawa T 1984 Effects of dehydroepiandrosterone-sulphate (DHEA-S) administration on puerperal lactation and maternal prolactin and estradiol levels. *Nihon Sanka Fujinka Gakkai Zasshi* **36** 1935–1942.
- Babalola PA, Fitz NE, Gibbs RB, Flaherty PT, Li PK & Johnson DA 2012 The effect of the steroid sulfatase inhibitor (p-O-sulfamoyl)-tetradecanoyl tyramine (DU-14) on learning and memory in rats with selective lesion of septal-hippocampal cholinergic tract. *Neurobiology of Learning and Memory* **98** 303–310. (<https://doi.org/10.1016/j.nlm.2012.09.003>)
- Baud A & Flint J 2017 Identifying genes for neurobehavioral traits in rodents: progress and pitfalls. *Disease Models and Mechanisms* **10** 373–383. (<https://doi.org/10.1242/dmm.027789>)
- Bergink V, Burgerhout KM, Weigelt K, Pop VJ, de Wit H, Drexhage RC, Kushner SA & Drexhage HA 2013 Immune system dysregulation in first-onset postpartum psychosis. *Biological Psychiatry* **73** 1000–1007. (<https://doi.org/10.1016/j.biopsych.2012.11.006>)
- Bergink V, Armangue T, Titulaer MJ, Markx S, Dalmau J & Kushner SA 2015 Autoimmune encephalitis in postpartum psychosis. *American Journal of Psychiatry* **172** 901–908. (<https://doi.org/10.1176/appi.ajp.2015.14101332>)
- Bergink V, Rasgon N & Wisner KL 2016 Postpartum psychosis: madness, mania, and melancholia in motherhood. *American Journal of*

- Psychiatry **173** 1179–1188. (<https://doi.org/10.1176/appi.ajp.2016.16040454>)
- Bird CE, Cook SJ, Dressel DE & Clark AF 1980 Plasma C19-delta 5-steroid levels during normal human pregnancy. *Clinical Biochemistry* **13** 126–128. ([https://doi.org/10.1016/S0009-9120\(80\)90795-X](https://doi.org/10.1016/S0009-9120(80)90795-X))
- Bridges RS 2015 Neuroendocrine regulation of maternal behavior. *Frontiers in Neuroendocrinology* **36** 178–196. (<https://doi.org/10.1016/j.yfrne.2014.11.007>)
- Brookes KJ, Hawi Z, Park J, Scott S, Gill M & Kent L 2010 Polymorphisms of the steroid sulfatase (STS) gene are associated with attention deficit hyperactivity disorder and influence brain tissue mRNA expression. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **153B** 1417–1424. (<https://doi.org/10.1002/ajmg.b.31120>)
- Buckwalter JG, Stanczyk FZ, McCleary CA, Bluestein BW, Buckwalter DK, Rankin KP, Chang L & Goodwin TM 1999 Pregnancy, the postpartum, and steroid hormones: effects on cognition and mood. *Psychoneuroendocrinology* **24** 69–84. ([https://doi.org/10.1016/S0306-4530\(98\)00044-4](https://doi.org/10.1016/S0306-4530(98)00044-4))
- Buster JE, Chang RJ, Preston DL, Elashoff RM, Cousins LM, Abraham GE, Hobel CJ & Marshall JR 1979 Interrelationships of circulating maternal steroid concentrations in third trimester pregnancies. II. C18 and C19 steroids: estradiol, estriol, dehydroepiandrosterone, dehydroepiandrosterone sulfate, delta 5-androstenediol, delta 4-androstenedione, testosterone, and dihydrotestosterone. *Journal of Clinical Endocrinology and Metabolism* **48** 139–142. (<https://doi.org/10.1210/jcem-48-1-139>)
- Carruthers SP, Gurvich CT & Rossell SL 2015 The muscarinic system, cognition and schizophrenia. *Neuroscience and Biobehavioral Reviews* **55** 393–402. (<https://doi.org/10.1016/j.neubiorev.2015.05.011>)
- Chatterjee S, Humby T & Davies W 2016 Behavioral and psychiatric phenotypes in men and boys with x-linked ichthyosis: evidence from a worldwide online survey. *PLoS ONE* **11** e0164417. (<https://doi.org/10.1371/journal.pone.0164417>)
- Corpechot C, Robel P, Axelsson M, Sjövall J & Baulieu EE 1981 Characterization and measurement of dehydroepiandrosterone sulfate in rat brain. *PNAS* **78** 4704–4707. (<https://doi.org/10.1073/pnas.78.8.4704>)
- Craig WY, Roberson M, Palomaki GE, Shackleton CH, Marcos J & Haddow JE 2010 Prevalence of steroid sulfatase deficiency in California according to race and ethnicity. *Prenatal Diagnosis* **30** 893–898. (<https://doi.org/10.1002/pd.2588>)
- Cuevas-Covarrubias SA, Juarez-Oropeza MA, Miranda-Zamora R & Diaz-Zagoya JC 1993 Comparative analysis of human steroid sulfatase activity in prepubertal and postpubertal males and females. *Biochemistry and Molecular Biology International* **30** 691–695.
- Cuevas-Covarrubias SA, Valdes-Flores M, Orozco Orozco E, Diaz-Zagoya JC & Kofman-Alfaro SH 1999 Most “sporadic” cases of X-linked ichthyosis are not de novo mutations. *Acta Dermatovenereologica* **79** 143–144. (<https://doi.org/10.1080/000155599750011381>)
- Davies W 2012 Does steroid sulfatase deficiency influence postpartum psychosis risk? *Trends in Molecular Medicine* **18** 256–262. (<https://doi.org/10.1016/j.molmed.2012.03.001>)
- Davies W 2017 Understanding the pathophysiology of postpartum psychosis: challenges and new approaches. *World Journal of Psychiatry* **7** 77–88. (<https://doi.org/10.5498/wjp.v7.i2.77>)
- Davies W, Humby T, Kong W, Otter T, Burgoyne PS & Wilkinson LS 2009 Converging pharmacological and genetic evidence indicates a role for steroid sulfatase in attention. *Biological Psychiatry* **66** 360–367. (<https://doi.org/10.1016/j.biopsych.2009.01.001>)
- Davies W, Humby T, Trent S, Eddy JB, Ojarikre OA & Wilkinson LS 2014 Genetic and pharmacological modulation of the steroid sulfatase axis improves response control; comparison with drugs used in ADHD. *Neuropsychopharmacology* **39** 2622–2632. (<https://doi.org/10.1038/npp.2014.115>)
- Dias NJ & Selcer KW 2016 Steroid sulfatase in the human MG-63 preosteoblastic cell line: antagonistic regulation by glucocorticoids and NFkappaB. *Molecular and Cellular Endocrinology* **420** 85–96. (<https://doi.org/10.1016/j.mce.2015.11.029>)
- Dietsche B, Kircher T & Falkenberg I 2017 Structural brain changes in schizophrenia at different stages of the illness: a selective review of longitudinal magnetic resonance imaging studies. *Australian and New Zealand Journal of Psychiatry* **51** 500–508. (<https://doi.org/10.1177/0004867417699473>)
- Egerton A, Modinos G, Ferrera D & McGuire P 2017 Neuroimaging studies of GABA in schizophrenia: a systematic review with meta-analysis. *Translational Psychiatry* **7** e1147. (<https://doi.org/10.1038/tp.2017.124>)
- Farrar D, Tuffnell D, Neill J, Scally A & Marshall K 2014 Assessment of cognitive function across pregnancy using CANTAB: a longitudinal study. *Brain and Cognition* **84** 76–84. (<https://doi.org/10.1016/j.bandc.2013.11.003>)
- Fernandes NF, Janniger CK & Schwartz RA 2010 X-linked ichthyosis: an oculocutaneous genodermatosis. *Journal of the American Academy of Dermatology* **62** 480–485. (<https://doi.org/10.1016/j.jaad.2009.04.028>)
- Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, McGuire P & Sacchetti E 2011 Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neuroscience and Biobehavioral Reviews* **35** 1175–1185. (<https://doi.org/10.1016/j.neubiorev.2010.12.005>)
- Gammie SC, Driessen TM, Zhao C, Saul MC & Eisinger BE 2016 Genetic and neuroendocrine regulation of the postpartum brain. *Frontiers in Neuroendocrinology* **42** 1–17. (<https://doi.org/10.1016/j.yfrne.2016.05.002>)
- Gelman PL, Flores-Ramos M, Lopez-Martinez M, Fuentes CC & Grajeda JP 2015 Hypothalamic-pituitary-adrenal axis function during perinatal depression. *Neuroscience Bulletin* **31** 338–350. (<https://doi.org/10.1007/s12264-014-1508-2>)
- Gentile S 2005 The role of estrogen therapy in postpartum psychiatric disorders: an update. *CNS Spectrums* **10** 944–952. (<https://doi.org/10.1017/S1092852900010518>)
- Geyer J, Bakhaus K, Bernhardt R, Blaschka C, Dezhkam Y, Fietz D, Grosser G, Hartmann K, Hartmann ME, Neunzig J, et al. 2017 The role of sulfated steroid hormones in reproductive processes. *Journal of Steroid Biochemistry and Molecular Biology* **172** 207–221. (<https://doi.org/10.1016/j.jsmb.2016.07.002>)
- Gratton AM, Ye L, Brownfoot FC, Hannan NJ, Whitehead C, Cannon P, Deo M, Fuller PJ, Tong S & Kaitu'u-Lino TJ 2016 Steroid sulfatase is increased in the placentas and whole blood of women with early-onset preeclampsia. *Placenta* **48** 72–79. (<https://doi.org/10.1016/j.placenta.2016.10.008>)
- Hampson E, Phillips SD, Soares CN & Steiner M 2013 Steroid concentrations in antepartum and postpartum saliva: normative values in women and correlations with serum. *Biology of Sex Differences* **4** 7. (<https://doi.org/10.1186/2042-6410-4-7>)
- Harrison PJ 2015 Recent genetic findings in schizophrenia and their therapeutic relevance. *Journal of Psychopharmacology* **29** 85–96. (<https://doi.org/10.1177/0269881114553647>)
- Hill M, Parizek A, Klak J, Hampl R, Sulcova J, Havlikova H, Lapcik O, Bicikova M, Fait T, Kancheva R, et al. 2002 Neuroactive steroids, their precursors and polar conjugates during parturition and postpartum in maternal and umbilical blood: 3.3beta-hydroxy-5-ene steroids. *Journal of Steroid Biochemistry and Molecular Biology* **82** 241–250. ([https://doi.org/10.1016/S0960-0760\(02\)00188-7](https://doi.org/10.1016/S0960-0760(02)00188-7))
- Humby T, Cross ES, Messer L, Guerrero S & Davies W 2016 A pharmacological mouse model suggests a novel risk pathway for postpartum psychosis. *Psychoneuroendocrinology* **74** 363–370. (<https://doi.org/10.1016/j.psyneuen.2016.09.019>)
- Humby T, Fisher A, Allen C, Reynolds M, Hartman A, Giegling I, Rujescu D & Davies W 2017 A genetic variant within STS previously associated with inattention in boys with attention deficit

- hyperactivity disorder is associated with enhanced cognition in healthy adult males. *Brain and Behavior* **7** e00646. (<https://doi.org/10.1002/brb3.646>)
- Idkowiak J, Taylor AE, Subtil S, O'Neil DM, Vijzelaar R, Dias RP, Amin R, Barrett TG, Shackleton CH, Kirk JM, *et al.* 2016 Steroid sulfatase deficiency and androgen activation before and after puberty. *Journal of Clinical Endocrinology and Metabolism* **101** 2545–2553. (<https://doi.org/10.1210/jc.2015-4101>)
- Jiang M, Klein M, Zanger UM, Mohammad MK, Cave MC, Gaikwad NW, Dias NJ, Selcer KW, Guo Y, He J, *et al.* 2016 Inflammatory regulation of steroid sulfatase: a novel mechanism to control estrogen homeostasis and inflammation in chronic liver disease. *Journal of Hepatology* **64** 44–52. (<https://doi.org/10.1016/j.jhep.2015.07.022>)
- Jones I, Hamshire M, Nangle JM, Bennett P, Green E, Heron J, Segurado R, Lambert D, Holmans P, Corvin A, *et al.* 2007 Bipolar affective puerperal psychosis: genome-wide significant evidence for linkage to chromosome 16. *American Journal of Psychiatry* **164** 1099–1104. (<https://doi.org/10.1176/ajp.2007.164.7.1099>)
- Jones I, Chandra PS, Dazzan P & Howard LM 2014 Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the postpartum period. *Lancet* **384** 1789–1799. ([https://doi.org/10.1016/S0140-6736\(14\)61278-2](https://doi.org/10.1016/S0140-6736(14)61278-2))
- Kent L, Emerton J, Bhadravathi V, Weisblatt E, Pasco G, Willatt LR, McMahon R & Yates JR 2008 X-linked ichthyosis (steroid sulfatase deficiency) is associated with increased risk of attention deficit hyperactivity disorder, autism and social communication deficits. *Journal of Medical Genetics* **45** 519–524. (<https://doi.org/10.1136/jmg.2008.057729>)
- Kriz L, Bicikova M, Mohapl M, Hill M, Cerny I & Hampl R 2008 Steroid sulfatase and sulfuryl transferase activities in human brain tumors. *Journal of Steroid Biochemistry and Molecular Biology* **109** 31–39. (<https://doi.org/10.1016/j.jsmb.2007.12.004>)
- Kuijper EA, Ket JC, Caanen MR & Lambalk CB 2013 Reproductive hormone concentrations in pregnancy and neonates: a systematic review. *Reproductive BioMedicine Online* **27** 33–63. (<https://doi.org/10.1016/j.rbmo.2013.03.009>)
- Kumar HB, Purushottam M, Kubendran S, Gayathri P, Mukherjee O, Murthy AR, Ghosh S, Chandra P, Reddy YC, Benegal V, *et al.* 2007 Serotonergic candidate genes and puerperal psychosis: an association study. *Psychiatric Genetics* **17** 253–260. (<https://doi.org/10.1097/YPG.0b013e3280ae6cc3>)
- Kumar MM, Venkataswamy MM, Sathyanarayanan G, Thippeswamy H, Chandra PS & Mani RS 2017 Immune system aberrations in postpartum psychosis: an immunophenotyping study from a tertiary care neuropsychiatric hospital in India. *Journal of Neuroimmunology* **310** 8–13. (<https://doi.org/10.1016/j.jneuroim.2017.06.002>)
- Langlois P, Armstrong L, Gall K, Hulait G, Livingston J, Nelson T, Power P, Pugash D, Siciliano D, Steinraths M, *et al.* 2009 Steroid sulfatase deficiency and contiguous gene deletion syndrome amongst pregnant patients with low serum unconjugated estriols. *Prenatal Diagnosis* **29** 966–974. (<https://doi.org/10.1002/pd.2326>)
- Lazaridis I, Charalampopoulos I, Alexaki VI, Avlonitis N, Padiaditakis I, Efsthathopoulos P, Calogeropoulou T, Castanas E & Gravanis A 2011 Neurosteroid dehydroepiandrosterone interacts with nerve growth factor (NGF) receptors, preventing neuronal apoptosis. *PLoS Biology* **9** e1001051. (<https://doi.org/10.1371/journal.pbio.1001051>)
- Lonstein JS, Levy F & Fleming AS 2015 Common and divergent psychobiological mechanisms underlying maternal behaviors in non-human and human mammals. *Hormones and Behavior* **73** 156–185. (<https://doi.org/10.1016/j.yhbeh.2015.06.011>)
- Lykkesfeldt G, Bennett P, Lykkesfeldt AE, Micic S, Moller S & Svenstrup B 1985 Abnormal androgen and estrogen metabolism in men with steroid sulphatase deficiency and recessive X-linked ichthyosis. *Clinical Endocrinology* **23** 385–393. (<https://doi.org/10.1111/j.1365-2265.1985.tb01096.x>)
- Maayan R, Abou-Kaud M, Strous RD, Kaplan B, Fisch B, Shinnar N & Weizman A 2004a The influence of parturition on the level and synthesis of sulfated and free neurosteroids in rats. *Neuropsychobiology* **49** 17–23. (<https://doi.org/10.1159/000075334>)
- Maayan R, Shaltiel G, Poyurovsky M, Ramadan E, Morad O, Nechmad A, Weizman A & Agam G 2004b Chronic lithium treatment affects rat brain and serum dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEA-S) levels. *International Journal of Neuropsychopharmacology* **7** 71–75. (<https://doi.org/10.1017/S1461145703003821>)
- Makieva S, Saunders PT & Norman JE 2014 Androgens in pregnancy: roles in parturition. *Human Reproduction Update* **20** 542–559. (<https://doi.org/10.1093/humupd/dmu008>)
- Malik A, Amer AB, Salama M, Haddad B, Alrifai MT, Al Balwi M, Davies W & Eyaid W 2017 X-linked ichthyosis associated with psychosis and behavioral abnormalities: a case report. *Journal of Medical Case Reports* **11** 267.
- Maninger N, Wolkowitz OM, Reus VI, Epel ES & Mellon SH 2009 Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). *Frontiers in Neuroendocrinology* **30** 65–91. (<https://doi.org/10.1016/j.yfrne.2008.11.002>)
- Marrs CR, Ferraro DP, Cross CL & Rogers SL 2009 A potential role for adrenal androgens in postpartum psychiatric distress. *European Journal of Obstetrics and Gynecology* **143** 127–128. (<https://doi.org/10.1016/j.ejogrb.2008.12.008>)
- Marrs CR, Ferraro DP & Cross CL 2010 Hormones and mood across the first postpartum year. *European Journal of Obstetrics and Gynecology* **149** 121–122. (<https://doi.org/10.1016/j.ejogrb.2009.11.006>)
- Meltzer HY, Massey BW & Horiguchi M 2012 Serotonin receptors as targets for drugs useful to treat psychosis and cognitive impairment in schizophrenia. *Current Pharmaceutical Biotechnology* **13** 1572–1586. (<https://doi.org/10.2174/138920112800784880>)
- Miki Y, Nakata T, Suzuki T, Darnel AD, Moriya T, Kaneko C, Hidaka K, Shiotsu Y, Kusaka H & Sasano H 2002 Systemic distribution of steroid sulfatase and estrogen sulfotransferase in human adult and fetal tissues. *Journal of Clinical Endocrinology and Metabolism* **87** 5760–5768. (<https://doi.org/10.1210/jc.2002-020670>)
- Milunsky J, Huang XL, Wyandt HE & Milunsky A 1999 Schizophrenia susceptibility gene locus at Xp22.3. *Clinical Genetics* **55** 455–460. (<https://doi.org/10.1034/j.1399-0004.1999.550610.x>)
- Miranda-Duarte A, Valdes-Flores M, Miranda-Zamora R, Diaz-Zagoya JC, Kofman-Alfaro SH & Cuevas-Covarrubias SA 1999 Steroid sulfatase activity in leukocytes: a comparative study in 45,X; 46,Xi(Xq) and carriers of steroid sulfatase deficiency. *Biochemistry and Molecular Biology International* **47** 137–142.
- Miyakawa I, Kawano Y, Taniyama K & Mori N 1994 Steroid sulfatase activity in human leukocytes. *Gynecologic and Obstetric Investigation* **38** 191–193. (<https://doi.org/10.1159/000292477>)
- Mortaud S, Donsez-Darcel E, Roubertoux PL & Degrelle H 1996 Murine steroid sulfatase gene expression in the brain during postnatal development and adulthood. *Neuroscience Letters* **215** 145–148. ([https://doi.org/10.1016/0304-3940\(96\)12944-X](https://doi.org/10.1016/0304-3940(96)12944-X))
- Mueller JW, Gilligan LC, Idkowiak J, Arlt W & Foster PA 2015 The regulation of steroid action by sulfation and desulfation. *Endocrine Reviews* **36** 526–563. (<https://doi.org/10.1210/er.2015-1036>)
- Nakamura Y, Miki Y, Suzuki T, Nakata T, Darnel AD, Moriya T, Tazawa C, Saito H, Ishibashi T, Takahashi S, *et al.* 2003 Steroid sulfatase and estrogen sulfotransferase in the atherosclerotic human aorta. *American Journal of Pathology* **163** 1329–1339. ([https://doi.org/10.1016/S0002-9440\(10\)63492-X](https://doi.org/10.1016/S0002-9440(10)63492-X))
- Neunzig J & Bernhardt R 2014 Dehydroepiandrosterone sulfate (DHEAS) stimulates the first step in the biosynthesis of steroid hormones. *PLoS ONE* **9** e89727. (<https://doi.org/10.1371/journal.pone.0089727>)
- Nicolas LB, Pinoteau W, Papot S, Routier S, Guillaumet G & Mortaud S 2001 Aggressive behavior induced by the steroid sulfatase inhibitor

- COUMATE and by DHEAS in CBA/H mice. *Brain Research* **922** 216–222.
- Nicolas LB & Fry JP 2007 The steroid sulfatase inhibitor COUMATE attenuates rather than enhances access of dehydroepiandrosterone sulfate to the brain in the mouse. *Brain Research* **1174** 92–96. (<https://doi.org/10.1016/j.brainres.2007.07.078>)
- Nieschlag E, Walk T & Schindler AE 1974 Dehydroepiandrosterone (DHA) and DHA-sulphate during pregnancy in maternal blood. *Hormone and Metabolic Research* **6** 170–171. (<https://doi.org/10.1055/s-0028-1095706>)
- Olincy A & Freedman R 2012 Nicotinic mechanisms in the treatment of psychotic disorders: a focus on the alpha7 nicotinic receptor. *Handbook of Experimental Pharmacology* **213** 211–232. (https://doi.org/10.1007/978-3-642-25758-2_8)
- Pawluski JL, Lonstein JS & Fleming AS 2017 The neurobiology of postpartum anxiety and depression. *Trends in Neurosciences* **40** 106–120. (<https://doi.org/10.1016/j.tins.2016.11.009>)
- Peixoto C, Devicari Cheda JN, Nardi AE, Veras AB & Cardoso A 2014 The effects of dehydroepiandrosterone (DHEA) in the treatment of depression and depressive symptoms in other psychiatric and medical illnesses: a systematic review. *Current Drug Targets* **15** 901–914. (<https://doi.org/10.2174/1389450115666140717111116>)
- Peixoto C, Carrilho CG, Barros JA, Ribeiro TT, Silva LM, Nardi AE, Cardoso A & Veras AB 2017 The effects of dehydroepiandrosterone on sexual function: a systematic review. *Climacteric* **20** 129–137. (<https://doi.org/10.1080/13697137.2017.1279141>)
- Perumal AS & Robins E 1973 Regional and subcellular distribution of aryl- and steroid sulfatases in brain. *Brain Research* **59** 349–358. ([https://doi.org/10.1016/0006-8993\(73\)90273-4](https://doi.org/10.1016/0006-8993(73)90273-4))
- Pluchino N, Drakopoulos P, Bianchi-Demicheli F, Wenger JM, Petignat P & Genazzani AR 2015 Neurobiology of DHEA and effects on sexuality, mood and cognition. *Journal of Steroid Biochemistry and Molecular Biology* **145** 273–280. (<https://doi.org/10.1016/j.jsmb.2014.04.012>)
- Purohit A & Foster PA 2012 Steroid sulfatase inhibitors for estrogen- and androgen-dependent cancers. *Journal of Endocrinology* **212** 99–110. (<https://doi.org/10.1530/JOE-11-0266>)
- Qaiser MZ, Dolman DEM, Begley DJ, Abbott NJ, Cazacu-Davidescu M, Corol DI & Fry JP 2017 Uptake and metabolism of sulphated steroids by the blood-brain barrier in the adult male rat. *Journal of Neurochemistry* **142** 672–685. (<https://doi.org/10.1111/jnc.14117>)
- Quilter CR, Blott SC, Wilson AE, Bagga MR, Sargent CA, Oliver GL, Southwood OI, Gilbert CL, Mileham A & Affara NA 2007 Porcine maternal infanticide as a model for puerperal psychosis. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **144B** 862–868. (<https://doi.org/10.1002/ajmg.b.30529>)
- Reed MJ, Purohit A, Woo LW, Newman SP & Potter BV 2005 Steroid sulfatase: molecular biology, regulation, and inhibition. *Endocrine Reviews* **26** 171–202. (<https://doi.org/10.1210/er.2004-0003>)
- Rhodes ME, Li PK, Flood JF & Johnson DA 1996 Enhancement of hippocampal acetylcholine release by the neurosteroid dehydroepiandrosterone sulfate: an in vivo microdialysis study. *Brain Research* **733** 284–286. ([https://doi.org/10.1016/0006-8993\(96\)00751-2](https://doi.org/10.1016/0006-8993(96)00751-2))
- Rhodes ME, Li PK, Burke AM & Johnson DA 1997 Enhanced plasma DHEAS, brain acetylcholine and memory mediated by steroid sulfatase inhibition. *Brain Research* **773** 28–32. ([https://doi.org/10.1016/S0006-8993\(97\)00867-6](https://doi.org/10.1016/S0006-8993(97)00867-6))
- Riecher-Rossler A 2017 Estrogens, prolactin, hypothalamic-pituitary-gonadal axis, and schizophrenic psychoses. *Lancet Psychiatry* **4** 63–72. ([https://doi.org/10.1016/S2215-0366\(16\)30379-0](https://doi.org/10.1016/S2215-0366(16)30379-0))
- Rutkowski K, Sowa P, Rutkowska-Talipska J, Kuryliszyn-Moskal A & Rutkowski R 2014 Dehydroepiandrosterone (DHEA): hopes and hopes. *Drugs* **74** 1195–1207. (<https://doi.org/10.1007/s40265-014-0259-8>)
- Salido EC, Yen PH, Barajas L & Shapiro LJ 1990 Steroid sulfatase expression in human placenta: immunocytochemistry and in situ hybridization study. *Journal of Clinical Endocrinology and Metabolism* **70** 1564–1567. (<https://doi.org/10.1210/jcem-70-6-1564>)
- Salman ED, Faye-Petersen O & Falany CN 2011 Hydroxysteroid sulfotransferase 2B1b expression and localization in normal human brain. *Hormone Molecular Biology and Clinical Investigation* **8** 445–454.
- Schury K, Koenig AM, Isele D, Hulbert AL, Krause S, Umlauf M, Kolassa S, Ziegenhain U, Karabatsiakis A, Reister F, et al. 2017 Alterations of hair cortisol and dehydroepiandrosterone in mother-infant-dyads with maternal childhood maltreatment. *BMC Psychiatry* **17** 213. (<https://doi.org/10.1186/s12888-017-1367-2>)
- Selvaraj S, Arnone D, Cappai A & Howes O 2014 Alterations in the serotonin system in schizophrenia: a systematic review and meta-analysis of postmortem and molecular imaging studies. *Neuroscience and Biobehavioral Reviews* **45** 233–245. (<https://doi.org/10.1016/j.neubiorev.2014.06.005>)
- Sexton MB, Hamilton L, McGinnis EW, Rosenblum KL & Muzik M 2015 The roles of resilience and childhood trauma history: main and moderating effects on postpartum maternal mental health and functioning. *Journal of Affective Disorders* **174** 562–568. (<https://doi.org/10.1016/j.jad.2014.12.036>)
- Shapiro LJ, Mohandas T, Weiss R & Romeo G 1979 Non-inactivation of an x-chromosome locus in man. *Science* **204** 1224–1226. (<https://doi.org/10.1126/science.156396>)
- Sharma V & Sommerdyk C 2015 Obsessive-compulsive disorder in the postpartum period: diagnosis, differential diagnosis and management. *Womens Health* **11** 543–552. (<https://doi.org/10.2217/WHE.15.20>)
- Skalkidou A, Hellgren C, Comasco E, Sylven S & Sundstrom Poromaa I 2012 Biological aspects of postpartum depression. *Womens Health* **8** 659–672. (<https://doi.org/10.2217/WHE.12.55>)
- Soares CN & Phillips SD 2006 Hormones in the treatment of depression. *Womens Health* **2** 435–445. (<https://doi.org/10.2217/17455057.2.3.435>)
- Soldin OP, Guo T, Weiderpass E, Tractenberg RE, Hilakivi-Clarke L & Soldin SJ 2005 Steroid hormone levels in pregnancy and 1 year postpartum using isotope dilution tandem mass spectrometry. *Fertility and Sterility* **84** 701–710. (<https://doi.org/10.1016/j.fertnstert.2005.02.045>)
- Soma KK, Rendon NM, Boonstra R, Albers HE & Demas GE 2015 DHEA effects on brain and behavior: insights from comparative studies of aggression. *Journal of Steroid Biochemistry and Molecular Biology* **145** 261–272. (<https://doi.org/10.1016/j.jsmb.2014.05.011>)
- Speisman BB, Storch EA & Abramowitz JS 2011 Postpartum obsessive-compulsive disorder. *Journal of Obstetric, Gynecologic, and Neonatal Nursing* **40** 680–690. (<https://doi.org/10.1111/j.1552-6909.2011.01294.x>)
- Starka L, Duskova M & Hill M 2015 Dehydroepiandrosterone: a neuroactive steroid. *Journal of Steroid Biochemistry and Molecular Biology* **145** 254–260. (<https://doi.org/10.1016/j.jsmb.2014.03.008>)
- Steckelbroeck S, Nassen A, Ugele B, Ludwig M, Watzka M, Reissinger A, Clusmann H, Lutjohann D, Siekmann L, Klingmuller D, et al. 2004 Steroid sulfatase (STS) expression in the human temporal lobe: enzyme activity, mRNA expression and immunohistochemistry study. *Journal of Neurochemistry* **89** 403–417.
- Stergiakouli E, Langley K, Williams H, Walters J, Williams NM, Suren S, Giegling I, Wilkinson LS, Owen MJ, O'Donovan MC, et al. 2011 Steroid sulfatase is a potential modifier of cognition in attention deficit hyperactivity disorder. *Genes, Brain and Behavior* **10** 334–344. (<https://doi.org/10.1111/j.1601-183X.2010.00672.x>)
- Stewart DE & Vigod S 2016 Postpartum depression. *New England Journal of Medicine* **375** 2177–2186. (<https://doi.org/10.1056/NEJMcp1607649>)

- Strous RD, Spivak B, Yoran-Hegesh R, Maayan R, Averbuch E, Kotler M, Mester R & Weizman A 2001 Analysis of neurosteroid levels in attention deficit hyperactivity disorder. *International Journal of Neuropsychopharmacology* **4** 259–264.
- Tagawa N, Hidaka Y, Takano T, Shimaoka Y, Kobayashi Y & Amino N 2004 Serum concentrations of dehydroepiandrosterone and dehydroepiandrosterone sulfate and their relation to cytokine production during and after normal pregnancy. *Clinica Chimica Acta* **340** 187–193. (<https://doi.org/10.1016/j.cccn.2003.10.018>)
- Tal R, Taylor HS, Burney RO, Mooney SB & Giudice LC 2000 Endocrinology of pregnancy. In *Endotext*. Eds LJ De Groot, G Chrousos, K Dungan, KR Feingold, A Grossman, JM Hershman, C Koch, M Korbonits, R McLachlan, M New, *et al.* MDText.com, Inc.:South Dartmouth, MA.
- Trent S & Davies W 2013 Cognitive, behavioral and psychiatric phenotypes associated with steroid sulfatase deficiency. *World Journal of Translational Medicine* **2** 1–12. (<https://doi.org/10.5528/wjtm.v2.i1.1>)
- Trent S, Cassano T, Bedse G, Ojarikre OA, Humby T & Davies W 2012a Altered serotonergic function may partially account for behavioral endophenotypes in steroid sulfatase-deficient mice. *Neuropsychopharmacology* **37** 1267–1274. (<https://doi.org/10.1038/npp.2011.314>)
- Trent S, Dennehy A, Richardson H, Ojarikre OA, Burgoyne PS, Humby T & Davies W 2012b Steroid sulfatase-deficient mice exhibit endophenotypes relevant to attention deficit hyperactivity disorder. *Psychoneuroendocrinology* **37** 221–229. (<https://doi.org/10.1016/j.psyneuen.2011.06.006>)
- Trent S, Dean R, Veit B, Cassano T, Bedse G, Ojarikre OA, Humby T & Davies W 2013 Biological mechanisms associated with increased perseveration and hyperactivity in a genetic mouse model of neurodevelopmental disorder. *Psychoneuroendocrinology* **38** 1370–1380. (<https://doi.org/10.1016/j.psyneuen.2012.12.002>)
- Ugele B & Regemann K 2000 Differential increase of steroid sulfatase activity in XX and XY trophoblast cells from human term placenta with syncytia formation in vitro. *Cytogenetics and Cell Genetics* **90** 40–46. (<https://doi.org/10.1159/000015657>)
- VanderKruik R, Barreix M, Chou D, Allen T, Say L, Cohen LS & Maternal Morbidity Working G 2017 The global prevalence of postpartum psychosis: a systematic review. *BMC Psychiatry* **17** 272. (<https://doi.org/10.1186/s12888-017-1427-7>)
- Vukadinovic Z 2014 NMDA receptor hypofunction and the thalamus in schizophrenia. *Physiology and Behavior* **131** 156–159. (<https://doi.org/10.1016/j.physbeh.2014.04.038>)
- Wang LJ, Chan WC, Chou MC, Chou WJ, Lee MJ, Lee SY, Lin PY, Yang YH & Yen CF 2017 Polymorphisms of STS gene and SULT2A1 gene and neurosteroid levels in Han Chinese boys with attention-deficit/hyperactivity disorder: an exploratory investigation. *Scientific Reports* **7** 45595. (<https://doi.org/10.1038/srep45595>)
- Yen PH, Marsh B, Allen E, Tsai SP, Ellison J, Connolly L, Neiswanger K & Shapiro LJ 1988 The human X-linked steroid sulfatase gene and a Y-encoded pseudogene: evidence for an inversion of the Y chromosome during primate evolution. *Cell* **55** 1123–1135. ([https://doi.org/10.1016/0092-8674\(88\)90257-7](https://doi.org/10.1016/0092-8674(88)90257-7))
- Yue XH, Tong JQ, Wang ZJ, Zhang J, Liu X, Liu XJ, Cai HY & Qi JS 2016 Steroid sulfatase inhibitor DU-14 protects spatial memory and synaptic plasticity from disruption by amyloid beta protein in male rats. *Hormones and Behavior* **83** 83–92. (<https://doi.org/10.1016/j.yhbeh.2016.05.019>)

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