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Review

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Maternally derived hormones, neurosteroids and the development of behaviour

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In a wide range of taxa, there is evidence that mothers adaptively shape the development of offspring behaviour by exposing them to steroids. These maternal effects have major implications for fitness because, by shaping early development, they can permanently alter how offspring interact with their environment. However, theory on parent–offspring conflict and recent physiological studies showing that embryos rapidly metabolize maternal steroids have placed doubt on the adaptive significance of these hormone-mediated maternal effects. Reconciling these disparate perspectives requires a mechanistic understanding of the pathways by which maternal steroids can influence neural development. Here, we highlight recent advances in developmental neurobiology and psychiatric pharmacology to show that maternal steroid metabolites can have direct neuro-modulatory effects potentially shaping the development of neural circuitry underlying ecologically relevant behavioural traits. The recognition that maternal steroids can act through a neurosteroid pathway has critical implications for our understanding of the ecology and evolution of steroid-based maternal effects. Overall, compared to the classic view, a neurosteroid mechanism may reduce the evolutionary lability of hormone-mediated maternal effects owing to increased pleiotropic constraints and frequently influence long-term behavioural phenotypes in offspring.

1. Introduction

Across diverse taxa, maternal allocation of steroid hormones to developing offspring varies with environmental conditions and is linked to adaptive adjustment of offspring phenotypes, including behavioural traits (birds [1,2], mammals [3–5], reptiles [6] and fishes [7]). By shaping key evolutionary and demographic processes, such hormone-mediated maternal effects have major consequences for fitness in wild populations [2,8–12]. However, theory suggests mothers and offspring may be engaged in a coevolutionary conflict with each side evolving different strategies to either resist or manipulate the other [13–15]. In this view, if maternally derived steroids are detrimental to offspring fitness, selection should favour offspring that can dismantle maternal hormones, thus inhibiting the evolution of adaptive hormone-mediated maternal effects [16].

Empirical studies examining the links between maternal steroids and offspring traits have yielded mixed results without resolving these conflicting ideas. On one hand, exposure of offspring to maternal steroids varies with environmental cues and is often correlated with the induction of ecologically relevant offspring phenotypes suggesting these maternal effects are adaptive (e.g. see [4,10]). On the other hand, recent physiological studies demonstrate that embryos rapidly metabolize maternal steroids into supposedly inert forms before they reach the developing embryo [17–21]. Because these steroid metabolites do not bind with classical steroid receptors, it suggests that embryos may 'win' in parent–offspring conflict by buffering themselves from maternal control

[13,14]. This raises new questions about the physiological mechanism through which maternally derived steroids might alter offspring traits and, more generally, the adaptive function of variation in maternal steroids. Here, we draw on recent advances in developmental neurobiology and psychiatric pharmacology to help answer these questions. We show that metabolized, and presumably deactivated, maternal hormones can impact the development of neuroendocrine circuits in offspring through neurosteroid pathways. Neurosteroid mechanisms may be the primary or an important supplemental pathway by which maternal steroids influence offspring phenotype, but have largely been ignored in the ecological literature (but see [17,22]). Integrating cutting-edge discoveries from these diverse fields provides insight into how maternal steroids can influence offspring behavioural phenotypes and has profound implications for our interpretation of the ecological and evolutionary consequences of maternally derived steroids.

2. The problem: embryonic metabolism of maternal steroids

Mothers expose their developing offspring to a suite of different steroid hormones, and it has long been assumed these hormones affect offspring phenotypes through the action of classical steroid receptors [16,23,24]. In this view, maternally derived steroids (e.g. testosterone) bind to steroid receptors in the embryo (e.g. androgen receptors) which can act as transcription factors, altering gene expression and, ultimately, the development of offspring phenotypes [25]. Yet, most maternal steroids are metabolized into compounds that are unable to bind to the receptors of their precursor steroids. For example, it has been shown in a variety of oviparous taxa that maternal testosterone levels rapidly decline in the yolk and albumen in the initial hours and days of incubation (chickens [18,22,26], European starlings [19,27], rock pigeons [17], zebra finches [28], Japanese quails [29] and red-eared slider turtles [30,31]). This decline does not reflect conversion to other steroids or uptake by the embryo. Studies that tracked radio-labelled testosterone in the egg generally find little to no conversion to other active steroids such as androstenedione, 5α-dihydrotestosterone, oestrogen or progesterone [17,18,22]. Instead, testosterone is generally metabolized into more polar, water-soluble forms such as etiocholanolone, which are often conjugated (e.g. bound to a sulfate group) further limiting their ability to bind to androgen receptors [17,18,22,27,31].

Similar metabolic pathways are observed for other maternal steroids. Androstenedione converts to etiocholanolone and its conjugates with little evidence of conversions to other biologically active steroids, such as testosterone or progesterone [17,18,32]. In both birds and mammals, progesterone is converted to pregnanolone or other similar forms which are often conjugated and do not act via progesterone, androgen, oestrogen or glucocorticoid receptors [17,19–21,30,31,33–35]. Glucocorticoids are also rapidly metabolized, producing more polar, conjugated forms (birds [22,36], mammals [37] and reptiles [38]). Several studies which injected labelled oestradiol into eggs at oviposition found rapid and steady declines over time and evidence it is converted to conjugated forms [19,30]. While there has been some evidence for increases in oestrogen in yolk over time in several species [26,29,39], this may derive from early endogenous production by the embryo rather than the conversion of maternal steroids [40,41]. Thus, recent studies have found a remarkably consistent pattern of maternal steroids being metabolized into compounds which do not bind with the classical steroid receptors.

Are embryos actively metabolizing maternal steroids before they can be directly exposed to them? Several studies in oviparous species have shown that the metabolism of maternal steroids only occurs (or occurs at much higher rates) in eggs with live embryos than infertile eggs or eggs with dead embryos [20,28,36]. This indicates that embryos are actively producing the enzymes that metabolize maternal steroids. The rapid metabolism of maternal steroids in the yolk and the difficulty of lipophilic steroids to be transported into the more aqueous embryo suggests that little active maternal steroid can act directly on embryonic tissues [23,42]. Indeed, studies examining the location and metabolism of labelled steroids in eggs find most is metabolized prior to entry into the embryo [18,19,36,43].

Still, the direct effects of maternal steroids through classical steroid receptors cannot be completely ruled out. First, small quantities of free steroid can make it to the embryo. Studies injecting chicken eggs with labelled corticosterone show that, while small amounts of labelled corticosterone are mostly metabolized, higher injection doses result in greater quantities of corticosterone in embryos 6 days later [43]. Second, a recent study found steroid receptors were expressed in extra-embryonic membranes when free steroids were still found in the yolk [44]. These receptors are in a prime location to be activated by steroids given their proximity to the yolk. However, the action of these receptors is unknown and may simply regulate the metabolism of maternal steroids rather than mediate effects on offspring phenotype. Finally, sulfate-conjugated hormones that move into the embryo may be converted back into active steroids [42]. Steroid sulfatase, an enzyme that conjugates steroids by adding a sulfate group, is reversible and is expressed widely in embryonic tissues across developmental stages [45]. Such conversions are particularly interesting because steroid sulphatase is X-linked in some taxa which could help explain the prevalence of sex-specific phenotypic effects of maternal steroids [1,46]. Still, further conversions involving other enzymes would be required to convert, for example, etiocholanolone sulfate back into testosterone and allow action via androgen receptors; it remains unclear whether such conversions are possible. Thus, while embryonic metabolism of maternal steroids may enable transport of lipophilic steroids to the aqueous environment of the embryo, the mechanisms underlying the ultimate actions of maternal steroids remain unclear.

Thus, while current studies don't completely rule out the idea of a direct action of maternally derived steroids, taken together, they suggest that our current model for how maternal steroids affect offspring phenotype may be incomplete. How can we reconcile the seeming inactivation of maternal steroids with ecological studies that not only provide evidence that offspring traits are affected by them, but also suggest these effects are refined adaptations to environmental variation (e.g. [4,9,10])? Intriguingly, many of these steroid metabolites are neuroactive steroids (hereafter neurosteroids) that mediate important neural and developmental processes, many of which may underlie the commonly observed correlations between maternal steroid allocation and phenotypic effects in offspring (figure 1*a*).

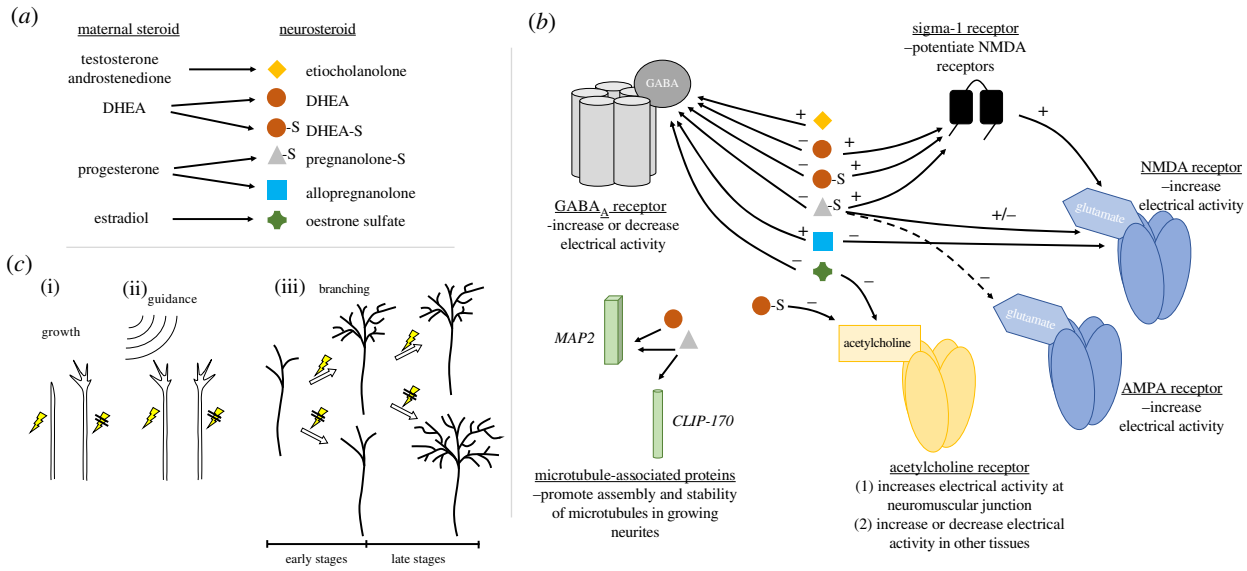

Figure 1. A neurosteroid pathway for the phenotypic effects of maternal steroids. (*a*) Many maternal steroids are converted into neurosteroid metabolites that do not bind with classical receptors. (*b*) However, these neurosteroid metabolites can bind with neurotransmitter receptors and microtubule-associated proteins and modulate their activity. (*c*) Variation in the activity of developing neural circuits can, for example, (i) alter neuron outgrowth, (ii) influence the response of growing neurites to chemical guidance cues, and (iii) promote or inhibit axon branching depending on the developmental stage. Modulation of these key neural processes via maternally derived neurosteroids may underlie effects of maternal steroids on long-term variation in behaviour by shaping the size or connectivity of neural circuits in different brain regions. Panel (*c*) is adapted from [67] © 2012 The Authors. European Journal of Neuroscience © 2012 Federation of European Neuroscience Societies and Blackwell Publishing Ltd.

3. Maternal steroids as precursors for neurosteroids

Neurosteroids are steroids that influence the activity of neurons in the short-term via non-genomic pathways (i.e. without directly altering gene expression). There are many types of neurosteroids that modulate neural activity in different ways (figure 1*b*). For example, they can bind to specific allosteric sites on multiple key neurotransmitter receptors (e.g. GABA$_A$, N-methyl-D-aspartate (NMDA)) [47]. By binding to allosteric sites, which are separate from the main active site, neurosteroids can affect sensitivity to neurotransmitters without creating interference at the active site. Thus, neurosteroids have important roles in modulating the sensitivity to neurotransmitters and affecting their activity and ultimately influence multiple neural processes including neuroprotection, myelination, outgrowth of neurites and dendritic spines and synaptogenesis (figure 1*c*) [48–53]. Through their effects on these cellular processes, neurosteroids can influence the size and connectivity of neural circuits in the brain and thereby shape long-term offspring behavioural traits. Neurosteroid actions on the central nervous system can also explain the effects of maternal steroids on ecologically relevant non-behavioural traits such as somatic growth, metabolic rate and immune function (see below). Below, we focus on how neurosteroid actions during development may adaptively shape brain structure and function by highlighting one well studied molecular interaction: neurosteroid modulation of GABA$_A$ receptors.

(a) Detailed mechanisms of neurosteroids on GABA$_A$ receptors

GABA$_A$ receptors, which are located in the plasma membrane of nerve terminals, glial cells and other somatic tissues, are activated by γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in vertebrates. Action of GABA on these receptors decreases the likelihood of post-synaptic electrical activity in neural circuits. Neurosteroids, including those created from maternal steroid precursors, can increase or decrease the receptor's affinity for GABA, thereby altering the likelihood of action potentials [53,54], neural activity, and may have major implications for the developing nervous system [55–62].

Already, in very early stages of embryonic development, electrical activity is produced by neurons and GABA$_A$ receptors are expressed in neurons across tissues [63–68]. In these early stage embryos, spontaneous neural activity, which is not triggered by environmental stimuli, is essential for key developmental processes including neural tube formation, neurogenesis, cell migration, programmed cell death, cellular differentiation and the formation of local and long-range neural connections [66,68–71]. Electrical activity in developing neurons can also influence cell growth and neurite branching as well as modulate responses to chemical guidance cues, which may have major implications for the degree and strength of connectivity in neural circuits important for behaviour (figure 1*c*,*d*) [66]. This electrical activity can be influenced by neurosteroid modulation of neurotransmitter receptors such as GABA$_A$ receptors, with wide-ranging consequences for the structure and function of brain tissue and the development of behaviour later in life. For example, guinea pigs that had reduced exposure to allopregnanolone (a placenta-derived neurosteroid) *in utero* were more likely to exhibit anxiety-like behaviour [72]. Similarly, exposure to neurosteroids in neonatal rats reduced the negative long-term behavioural and neuroendocrine consequences of maternal separation early in life [73]. Notably, the effects of neurosteroids on behaviour are often context-dependent (i.e. neurosteroid exposure effects vary with postnatal stress treatments) and sex-specific which mirrors findings regarding maternal steroid effects from the ecological literature [72,74,75]. In humans, reduced exposure

to placental neurosteroids *in utero* is linked to a greater risk of developing attention deficit hyperactivity disorder, anxiety and other long-term behavioural consequences of pre-term birth [57,60,61]. Together, these findings strongly support the idea that maternally derived neurosteroids influence electrical activity in neurons and are essential for the normal development of neural function and behaviour.

While neurosteroids have clear implications for brain function and behaviour, neurosteroid actions on $GABA_A$ receptors may also indirectly influence other tissues that are frequently associated with non-behavioural responses to maternal steroids. For example, many studies have found that embryonic exposure to testosterone is associated with muscular and skeletal growth [1,4]. Electrical activity in developing neurons, which can be sensitive to neurosteroid modulation, is important for forming neural tissue connections in these tissues [76]. For instance, $GABA_A$ receptors are found in skeletal muscle and GABAergic activity regulates muscle innervation in mice [77]. Neurosteroid-sensitive $GABA_A$ receptors also promote cell proliferation in rat tibial growth plates which are critical to long bone growth [78]. Maternal steroids are also known to influence offspring immune function, and, because $GABA_A$ receptors are expressed in many immune cells, immune effects may be modulated by neurosteroid metabolites of maternal steroids [1,79]. For example, $GABA_A$ receptors modulated the innate immune response in tissue cultures and GABAergic inhibition was associated with increased bacterial loads and host susceptibility in zebrafish and mice [79]. Additionally, GABA is implicated in multiple endocrine disorders, suggesting early neurosteroid actions on GABA activity could have direct effects on adrenal, thyroid, gonadal and somatic endocrine axes [80]. Such interactions may explain previously described steroid-mediated maternal effects on hormone sensitivity [81] and many other phenotypic traits including metabolic rate [82] and anti-oxidant status [83]. Clearly, the actions of neurosteroids derived from maternal hormones have the potential to shape the development of a diversity of offspring phenotypes including growth, immune and endocrine functions, beyond their clear potential for influencing neural connectivity and behaviour.

(b) Neurosteroids and adaptive programming of behaviour

Variation in maternally derived neurosteroids could adaptively shape specific neural circuits and influence the subtle or discrete phenotypic variation in adaptive offspring behaviour in several ways. First, developing neural circuits have discrete time periods ('sensitive windows' *sensu* [84]) when they proliferate, form connections and consolidate those connections. Neurosteroid modulation of neural activity could affect either the length of sensitive windows or the rate of activity-dependent processes during sensitive windows. Altering the duration of sensitive developmental windows may either enable or minimize the modulating effects of other inputs such as endogenously produced hormones acting via classical receptors [84,85]. Trade-offs between the size and connectivity of different neural circuits may yield smaller or less well connected neural circuitry in later developing regions [86]. For example, neurosteroids may cause increases in the space taken up by early developing circuits in the limbic system, which controls emotion, and limit the space available for the later developing neural circuits associated with higher level cortical functions such as decision-making [87,88]. Physical trade-offs between brain regions underlying these general functions are associated with many ecologically relevant behavioural traits, such as fearfulness and aggression [88,89].

Second, there are clear biologically relevant differences in how different metabolites of maternal steroids interact with developing neural networks (figure 1*b*) [51]. For example, allopregnanolone stimulates $GABA_A$ receptors, but dehydroepiandrosterone (DHEA) and DHEA-sulfate inhibit $GABA_A$ receptors, suggesting that the balance of these metabolites is important in regulating $GABA_A$ receptor activity [51]. This supports the view that maternal steroids should be considered from a multivariate perspective, as it is the interaction between the suite of maternally allocated steroids and their metabolites, rather than each in isolation, that are key to understanding phenotypic effects in offspring [15,17].

Finally, the effects of neurosteroids on synaptogenesis and neurite outgrowth could have implications for lateralization of various brain regions and functions [90]. For example, application of testosterone, oestrogens or corticosterone in chicken eggs prevents lateralization of thalamofugal vision projections normally caused by light stimuli during incubation [91]. Neurosteroid metabolites of these hormones might induce this effect by increasing neural activity in regions without light stimuli or decreasing neural activity caused by light stimuli. Birds lacking this lateralization show reduced foraging efficiency in the presence of a predator and showed more fearful behaviour when they detected a predator's presence [91]. These traits are typically associated with less bold behavioural types [92]. Lateralization is associated with behavioural traits with clear implications for fitness in other taxa as well (fish: [93], amphibians: [94] and mammals: [95,96]). Ultimately, the link between maternally derived neurosteroids, brain lateralization and behaviour demand further study.

4. Ecological and evolutionary implications

(a) Maternal hormones, sexual differentiation and pleiotropic constraint

One long-standing puzzle regarding the effects of maternal steroids on offspring is that they have little effect on sexual differentiation [97,98]. In birds and mammals, oestrogens androgens, and their receptors are essential for sexual differentiation of the gonads, reproductive tracts, brain and behaviour [97,99,100]. Yet, while biologically relevant variation in maternal sex steroids seems to have little or no effect on sexual differentiation, extremely high doses of sex steroids do influence sexual differentiation [23,97]. The knowledge that maternal steroids are rapidly metabolized prior to entering the embryos in conjunction with a neurosteroid mechanism of action resolves this seeming paradox. Maternally derived sex steroids that are immediately converted into neurosteroids will not interfere with sexual differentiation and still can influence offspring trait development. Unnaturally high doses of sex steroids used in some experiments may exceed the capacity for embryonic enzymes to convert them, leaving substantial amounts of unmetabolized steroids to reach the embryos and interfere with sexual differentiation. Together, these observations provide an explanation for why it may have been

necessary for indirect rather than direct effects of maternal steroids to evolve. A neurosteroid mechanism of action can eliminate the potential interference of steroids with sexual differentiation while still allowing adaptive adjustment of behaviour and other ecologically relevant traits. Thus, a neurosteroid mechanism may allow selection to shape adaptive maternal steroid allocation strategies more freely [100–102].

In contrast with effects on sexual differentiation, maternal steroids acting through a neurosteroid pathway may make it more difficult to decouple other ecologically relevant traits (e.g. somatic growth, aggression) compared to actions via steroid receptors. Classical hormone receptors can be expressed differentially across tissues and can be temporally disassociated from endogenous steroid production by the developing offspring [13,101,102]. For example, steroid receptors are expressed in some tissues before embryos begin producing steroids endogenously ([103], but see [40]). This is often taken as evidence for adaptation for steroid-mediated maternal effects because any remaining unmetabolized maternal steroid binding to these receptors would not interfere with important processes regulated by endogenous hormones (i.e. sexual differentiation). Additionally, the expression of steroid receptors may be able to increase or decrease in many tissues without major costs. For example, mutant mice that were entirely unable to express androgen receptors in their nervous system showed abnormal sexual behavioural, but nevertheless survived to reproductive maturity and produced offspring [104]. Thus, the evolution of steroid receptor distributions may be fairly labile, allowing selection to act rapidly in decoupling particular traits from the effects of maternal steroids if antagonistic selection favours novel trait combinations [15,101,102,105].

The activity of neurotransmitter-mediated ion channels, such as from $GABA_A$ receptors, are essential for normal functioning and development of the central nervous system even during the very earliest stages of life (e.g. neural tube formation, neurogenesis and neural cell migration [70]). In contrast with the mutant mouse example above [104], mutations dramatically altering expression patterns of these receptors are more likely to disrupt key GABA-binding related functions and result in catastrophic consequences very early in development (e.g. respiratory failure [106,107] and neural tube defects [71]). Moreover, given the relative stability of neural tissues, neurosteroid effects on neurogenesis, cell migration and neural connectivity seem more likely to contribute to long-term effects on these neural tissues and associated stable behavioural traits [84,89,108]. Thus, overall, co-expression of traits through a neurosteroid pathway may be more difficult to decouple than under the classical pathway owing to the widespread, primary and long-lasting effects of altered neural activity early in development.

(b) Evolution of hormone-mediated maternal effects as carry-over effects

Exposure to maternal hormones is known to affect both short-term and long-term phenotypes in offspring. For example, in birds, yolk androgens are linked to short-term traits expressed exclusively in early life stages (nestlings) such as growth and begging behaviours as well as long-term traits expressed across multiple later life stages such as aggression and sexual traits [1]. Consequently, a useful framework for addressing the evolution of hormone-mediated maternal effects is the evolution of carry-over effects where phenotypic traits expressed earlier in life are linked to the expression of phenotypic traits later in life [105,109]. Selection on carry-over effects may favour combinations of early (i.e. short-term) and late (i.e. long-term) expressed phenotypes that are either facilitated or constrained by shared underlying developmental pathways [101,102,105]. If directional selection on early and late expressed traits is concordant, the underlying pathway will evolve to shape both traits as a correlated suite. By contrast, under antagonistic selection, the nature of the underlying developmental pathway and the ecological significance of the associated phenotypic traits can have a major impact on their evolution. Given that phenotypic traits affected by the action of maternally derived neurosteroids might not be easily decoupled (see above), theory on the evolution of carry-over effects provides two principle insights [105].

First, the evolution of steroid-mediated maternal effects will depend on the relative strength of selection across early and late-life stages (or ages). When two traits face selection for different optima, a classic steroid receptor paradigm predicts that sensitivity of each trait to maternal steroids should evolve to allow optimal expression of both traits [13,101,102]. Under a neurosteroid-based pathway where traits cannot be easily dissociated, antagonistic selection may not be able to optimize both traits and the overall response to selection will depend on the strength of selection during early versus late-life stages and their relative contribution to fitness [105]. The strength of selection during any particular life stage depends on the selection gradient on fitness components during that stage and the relative contribution of distinct fitness components to lifetime reproductive success [105,110,111]. This means that the importance of selection on maternally derived neurosteroid linked traits depends directly on both the ontogenetic timing of trait expression and the life history and stage-structure of a given species or population. For example, survival during later life stages contributes more to fitness in longer-lived than shorter-lived species [110,112,113]. Thus, if accurate environmental cues are available, the selection on maternal neurosteroid-mediated traits that influence survival in adult life stages should be relatively stronger in longer-lived than shorter-lived species. In many cases, long-term traits expressed across multiple life stages may have an outsized effect on fitness. For example, maternal steroid effects on long-term behavioural traits, such as aggression, are often expressed before sexual maturity and influence survival over long periods of important pre-reproductive life stages as well as survival and fecundity in adult life stages [88,114]. In this case, selection may act more strongly on traits expressed over a longer duration and in life stages most critical for fitness. Consequently, adaptive maternal effects based on neurosteroid activity may be more likely to evolve in longer-term traits such as stable behavioural types while costs are more likely to be incurred through shorter-term traits. Comparative studies that examine how the fitness effects of maternal steroids in ecologically relevant conditions differ among species with distinct demographic traits are needed to test these ideas.

Second, strong antagonistic selection should act to dissociate both early and late expressed traits from environmental variation in maternally derived neurosteroids. If antagonistic selection on carry-over effects is strong and balanced across life stages, theory predicts over evolutionary timescales it will either (i) alter the sensitivity of each trait to the shared developmental pathway independently, (ii) dissociate the

developmental pathway from environmental conditions, or (iii) reduce the sensitivity of all offspring phenotypes linked to the shared developmental pathway [105]. The first scenario seems unlikely under a neurosteroid mechanism, given there may be greater constraints on receptor expression compared to a classical mechanism (see above). In the second case, variation in maternally derived steroids would evolve to become unrelated to environmental variation. The sensitivity of maternal steroid deposition to environmental cues, such as population density, are greater in some species (e.g. colonial breeders) than others (e.g. solitary breeders), potentially reflecting variation in antagonistic selection [115]. In the third case, offspring would prevent maternally derived neurosteroids from having any effects and instead rely on endogenously produced neurosteroids during development. This could manifest as the further metabolism of maternally derived neurosteroids into compounds that are not neuroactive or mechanisms to prevent maternally derived neurosteroids from accessing embryonic tissue. In either case, mechanisms for adaptive programming other than maternal steroid transfer may enable offspring traits to respond independently to maternal cues about the environment. Studies comparing environmental sensitivity of maternal steroid deposition (e.g. see [115]) and additional studies examining steroid metabolism by offspring in species with clear predictions about selective regimes will shine light on these issues.

(c) Parent–offspring conflict and coadaptation

Maternally derived hormones and offspring responses to those hormones have been proposed to be an important battleground for sexual and parent–offspring conflict because of traits such as offspring begging behaviours which can influence parental investment [1,13–16]. In this view, allocation of maternal steroids may increase fitness for mothers, but only at a cost to the fitness of individual offspring or, in species with paternal care, fathers [16]. The proposed neurosteroid mechanism of action for maternal steroids has several implications for this notion.

First, the idea that maternal steroids are central to parent–offspring conflict presupposes that the most important fitness effects of maternal steroids will occur during life stages with substantial parental investment [105,116]. Once offspring no longer receive costly care from their parents, the evolutionary interests of parents and offspring align with both favouring maximizing offspring lifetime reproductive success. A neurosteroid pathway acting on relatively stable neural tissues [89,108] may be more prone to shape long-term behavioural traits that face selective pressures across multiple life stages (see above). Because selection would be acting on these traits well after independence from parental care, this may reduce the importance of parent–offspring conflict. For example, selection on offspring that increases begging intensity to increase parental investment and fitness in the first week of life may be counteracted by selection for reduced aggression or dispersal propensity in later life stages. Moreover, young offspring in many species face high levels of mortality owing to extrinsic factors (e.g. predation, harsh weather, low food availability) that are more likely to be influenced by parental traits such as nest site selection than offspring traits expressed during early stages [117]. This may also cause selection on maternal neurosteroid linked offspring traits to become more important as offspring age.

Second, part of the reason why maternal allocation of steroids is thought to provide an arena for parent–offspring conflict is that selection can shape offspring responses to favour offspring instead of maternal fitness [13–16]. For example, offspring could express hormone receptors in the tissues and densities that favour offspring fitness at the expense of maternal fitness. From this perspective, the rapid manipulation of maternal steroids into compounds that do not bind to classical hormone receptors could be interpreted as evidence for offspring completely nullifying the effect of maternal steroids [13–16]. However, if maternally derived neurosteroids act directly on developing offspring neural circuits, the ability of offspring to actively resist the effect of maternal steroids may be more limited. Unlike hormone receptors which can be expressed or not in many tissues, the location and timing of expression of $GABA_A$ receptors, for example, may be less evolutionarily labile (see above, [71]). Thus, under a neurosteroid mechanism, responses to maternal steroids may be less likely to represent manipulative signals and more likely to represent the aligned interest of parents and offspring rather than a conflict over parental investment.

5. Future directions

In this review, we have drawn on recent work in behavioural ecology, developmental neurobiology and psychiatric pharmacology to highlight evidence that maternal steroids may act on offspring phenotypes via a neurosteroid pathway and explore its ecological and evolutionary consequences. Nonetheless, much work remains to be done to fully elucidate the neurosteroid-based mechanisms described here and understand their evolution. First, more research is needed to detail the physiological mechanisms underlying the effects of maternal hormones. Though several past experiments have examined the location of maternal steroid metabolites relative to the embryo [18,19,36,37], more studies are needed to trace different metabolites across tissues and throughout embryonic development. Such studies will improve our understanding of interactions between maternally derived steroids and neurotransmitter or classical steroid receptors. Second, a neurosteroid pathway also predicts that patterns of neuron activity, growth and connectivity will differ with variation in maternal hormones. Experiments that manipulate yolk steroids or steroid metabolites (e.g. [27]) and measure effects on electrical activity in embryos (e.g. microelectrode array recording [118]) or examine changes to the structure of neural circuits in brain sections would be helpful. Creative experiments involving chemicals that block neurosteroid production (e.g. finasteride [72]) may be useful in this context. Finally, the testing for a neurosteroid pathway demands (i) an increased focus on the long-term implications of maternal steroids in the context of structured populations and environmental variation, and (ii) comparative work that examines how populations or species differ in maternal steroid deposition under varied environmental conditions (e.g. [115]). Ultimately, while a neurosteroid pathway does not preclude the possibility of direct effects of maternal steroids through classical steroid receptors (see above), the presence of maternally derived neurosteroids in developing embryos suggests a neurosteroid pathway deserves more study. Examining the complex actions of maternal steroids during offspring development promises to

provide a richer understanding of adaptive maternal effects and the development of behaviour.

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