



# Steroid Transport, Local Synthesis, and Signaling within the Brain: Roles in Neurogenesis, Neuroprotection, and Sexual Behaviors

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Sex steroid hormones are synthesized from cholesterol and exert pleiotropic effects notably in the central nervous system. Pioneering studies from Baulieu and colleagues have suggested that steroids are also locally-synthesized in the brain. Such steroids, called neurosteroids, can rapidly modulate neuronal excitability and functions, brain plasticity, and behavior. Accumulating data obtained on a wide variety of species demonstrate that neurosteroidogenesis is an evolutionary conserved feature across fish, birds, and mammals. In this review, we will first document neurosteroidogenesis and steroid signaling for estrogens, progestagens, and androgens in the brain of teleost fish, birds, and mammals. We will next consider the effects of sex steroids in homeostatic and regenerative neurogenesis, in neuroprotection, and in sexual behaviors. In a last part, we will discuss the transport of steroids and lipoproteins from the periphery within the brain (and vice-versa) and document their effects on the blood-brain barrier (BBB) permeability and on neuroprotection. We will emphasize the potential interaction between lipoproteins and sex steroids, addressing the beneficial effects of steroids and lipoproteins, particularly HDL-cholesterol, against the breakdown of the BBB reported to occur during brain ischemic stroke. We will consequently highlight the potential anti-inflammatory, anti-oxidant, and neuroprotective properties of sex steroid and lipoproteins, these latest improving cholesterol and steroid ester transport within the brain after insults.

**Keywords:** aromatase, cholesterol, blood-brain barrier, estrogens, HDL, lipoproteins, stroke, progestins

## INTRODUCTION

Steroid hormones display important physiological functions and exert pleiotropic effects on many target organs including among others the gonads, the liver, and the nervous system. Neurosteroids are produced in the central nervous system (CNS), either via *de novo* synthesis from cholesterol or from local metabolism of steroid intermediate produced in the periphery. The shift from systemic to local synthesis and regulation of steroid action within target tissues, such as the brain, was referred to “Balkanization” of the endocrine system, and could allow the

tissue to autonomously synthesize and modulate local steroid signaling (Schmidt et al., 2008). Neurosteroids and peripherally produced steroids have pleiotropic effects and can modulate both brain homeostasis and cerebral functions. The aim of the present review is to summarize the current knowledge regarding the activity and the expression of the steroidogenic enzymes and the targets of steroids, produced in the periphery as well as locally in the brain. We will further consider the roles of androgens, estrogens, and progestagens on physiology and behavior, focusing our discussion on constitutive and regenerative neurogenesis, notably in stroke conditions, as well as the impact of these locally-produced sex steroids on sexual behavior. These points will be discussed from studies performed in fish, birds, and mammals from a comparative point of view. Furthermore, we will discuss the transport of peripheral steroids through the blood-brain barrier (BBB) and their effects on its permeability. We will emphasize the role of this transport by lipoproteins in the functioning of the BBB and during CNS insults, raising the question of the potential roles of cholesterol/steroid transport in neuroprotection and reactive neurogenesis.

## NEUROSTEROIDOGENESIS IN THE BRAIN: AN OVERVIEW IN FISH, BIRDS, AND MAMMALS

### Steroidogenesis

Steroidogenesis is the enzymatic process by which cholesterol is converted to biologically active steroid hormones. The steroidogenic acute regulatory protein (StAR), and translocator protein (TSPO), in a complex with various proteins including VDAC and ATAD3A, are involved in the transport of cholesterol to the inner membrane of the mitochondria. The first and rate-limiting enzymatic step of the steroidogenic process is the conversion of cholesterol into pregnenolone by P450 side chain cleavage (P450<sub>scc</sub>; CYP11A1). As shown in the steroidogenic pathway illustrated in **Figure 1**, pregnenolone can subsequently be converted into progesterone (P) by 3- $\beta$ -hydroxysteroid dehydrogenase (3 $\beta$ -HSD) or into 17-hydroxypregnenolone by 17- $\alpha$ -hydroxylase/17,20 lyase (CYP17). Then, CYP17 can convert progesterone into 17-hydroxyprogesterone, while 3 $\beta$ -HSD can convert 17-hydroxypregnenolone into 17-hydroxyprogesterone. In a next step, 17-hydroxypregnenolone and 17-hydroxyprogesterone can be converted by CYP17 into dehydroepiandrosterone (DHEA) and androstenedione, respectively. In turn, the activity of different 17 $\beta$ -HSD enzymes catalyzes the synthesis of androstenediol from DHEA and testosterone (T) from androstenedione. Aromatase converts androstenedione and testosterone into estrone (E1) and estradiol (E2), respectively, while 5 $\alpha$ -reductase converts testosterone into 5 $\alpha$ -dihydrotestosterone (DHT). Considering glucocorticoids, the synthesis of 11-deoxycortisol and 11-deoxycorticosterone from 17-hydroxyprogesterone and progesterone, respectively, are catalyzed by 21-hydroxylase (CYP21A2), followed by the P450C11 (Cyp11, cytochrome P450 11 $\beta$ -hydroxylase B1 and/or B2) activity leading to the synthesis of cortisol and

corticosterone. Cortisone can also be converted into cortisol by 11 $\beta$ -HSD.

### Steroidogenic Activities in the Brains of Fish

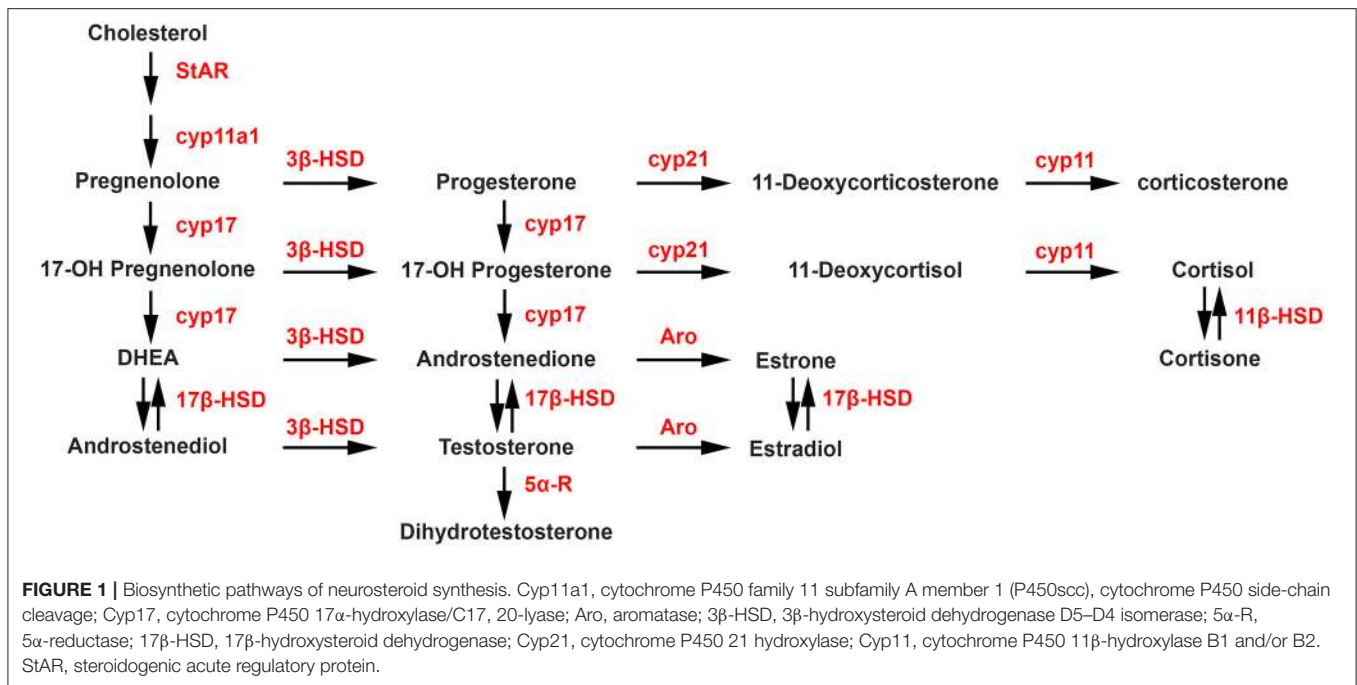
In the 80s, pioneering studies performed in the goldfish (*Carassius auratus*) and the toadfish (*Opsanus tau*) documented very high brain aromatase and 5 $\alpha$ -reductase activities (Pasmanik and Callard, 1985, 1988). High aromatase expression and activity in the brain is a common feature of teleost fish (Kah et al., 2009; Diotel et al., 2010), as reported in the African catfish (*Clarias gariepinus*) (Timmers and Lambert, 1987), the Atlantic Salmon (*Salmo salar*) (Andersson et al., 1988), the three-spined stickleback (*Gasterosteus aculeatus*) (Borg et al., 1989), the European sea bass (*Dicentrarchus labrax*) (Gonzalez and Piferrer, 2003), and the zebrafish (*Danio rerio*) (Goto-Kazeto et al., 2004; Diotel et al., 2011b). The high aromatase activity in the brain of fish is due to the sustained expression of the *cyp19a1b* gene coding for the Cyp19a1b/Aromatase B protein (AroB), while the *cyp19a1a* isoform coding for Cyp19a1a/Aromatase A protein is mainly expressed in gonads. These two isoforms likely resulted from a third round of genomic duplication event occurring ~320–350 million years ago in fish (Ravi and Venkatesh, 2008).

Biochemical studies using RP-HPLC analysis showed that the brains of adult zebrafish is able to convert [<sup>3</sup>H]-pregnenolone into [<sup>3</sup>H]-progesterone, documenting subsequently 3 $\beta$ -HSD activity in the brain of this teleost. These data were reinforced by the absence of progesterone synthesis following treatment with trilostane, a specific inhibitor of 3 $\beta$ -HSD (Sakamoto et al., 2001a). Ten years later, using similar methods, it was shown that the adult zebrafish brain can convert [<sup>3</sup>H]-pregnenolone into a wide variety of radiolabeled steroids including 17OH-pregnenolone, progesterone (P), and tetrahydro-P, DHEA, androstenedione, testosterone (T), dihydrotestosterone (DHT), 17 $\beta$ -estradiol (17 $\beta$ -E2), and also estrone (E1) (Diotel et al., 2011b). Expression and activity studies in the brain of adult zebrafish were documented for 3 $\alpha$ -Hsd, 3 $\beta$ -Hsd, 17 $\beta$ -Hsd, Cyp17, AroB, and 5 $\alpha$ -reductase (Diotel et al., 2011b). The recent reanalysis of the RP-HPLC profiles previously reported by Diotel et al. (2011a) indicated that [<sup>3</sup>H]-pregnenolone can also be converted into cortisol and tetrahydrodeoxycorticosterone (THDOC), further highlighting Cyp21A2 and Cyp11C1 activities within the brain of adult zebrafish (Weger et al., accepted).

Taken together, these data demonstrate that the brain of adult fish is able to *de novo* synthesize a wide variety of steroids from pregnenolone, suggesting that the substrates available for steroidogenesis can originate from local synthesis within the brain, and also from the conversion of peripherally produced precursors.

### Steroidogenic Enzyme Expression in the Brains of Fish

The first attempts to localize aromatase-expressing cells in the brain of fish were performed in goldfish using antibodies raised against human placental aromatase (Gelinias and Callard,



1997). In this work, neuron-like cells were labeled in the olfactory bulb, the telencephalon, the preoptic area, and the hypothalamus. However, *cyp19a1b* *in situ* hybridization and double immunohistochemistry using specific AroB antibodies and glial (GFAP, S100 $\beta$ , and BLBP) or neuronal markers (HuC/D or NeuN) clearly demonstrated the exclusive glial nature of AroB<sup>+</sup> cells in others teleost species (Forlano et al., 2001; Goto-Kazeto et al., 2004; Forlano and Bass, 2005; Strobl-Mazzulla et al., 2005; Pellegrini et al., 2007; Mouriec et al., 2008; Tong et al., 2009; März et al., 2010; Coumaillieu et al., 2015; Diotel et al., 2016). These data were further reinforced by the development of a *cyp19a1b*-GFP transgenic zebrafish line, showing the exclusive GFP co-expression with glial markers (Tong et al., 2009). Interestingly, AroB<sup>+</sup> cells correspond to radial glial cells (RGCs), a particular type of cells with a characteristic morphology. Radial glial cells display a soma localized in the vicinity of the ventricular layer and exhibit two cytoplasmic processes, a short one extending to the ventricle and a longer one running through the brain parenchyma toward the pial surface. In mammals, RGCs behave as neural stem cells (NSCs) during embryonic development and transform into astrocytes at the perinatal stage (Noctor et al., 2001; Weissman et al., 2003; Kriegstein and Alvarez-Buylla, 2009). In fish, they persist during adulthood and maintain neural progenitor properties (Adolf et al., 2006; Pellegrini et al., 2007, 2013, 2015; Tong et al., 2009; März et al., 2010; Rothenaigner et al., 2011; Kizil et al., 2012; Diotel et al., 2016).

Other studies performed in zebrafish documented the expression of 3 $\beta$ -Hsd in neuronal soma and fibers throughout the brain (i.e., dorsal telencephalon, thalamus, preoptic area, paraventricular organ), the cerebellum and the spinal cord

(Sakamoto et al., 2001a). In the African lungfish (*Protopterus annectens*), 3 $\beta$ -Hsd was also shown to be expressed in neurons while 5 $\alpha$ -reductase was detected in both glia and neurons (Mathieu et al., 2001). Furthermore, numerous experiments documented the expression of the steroidogenic enzymes (*P450scc*, *3 $\beta$ -hsd*, *cyp17*, and *cyp19a1b*) in the brains of fish including the Tongue sole (*Cynoglossus semilaevis*) and the Black porgy (*Acanthopagrus schlegeli*) (Tomy et al., 2007; Chen et al., 2010b). In adult zebrafish, *in situ* hybridization experiments indicate that there is a wide and overlapping distribution of *P450scc*, *3 $\beta$ -hsd*, *cyp17*, and *cyp19a1b* throughout the brain particularly in the telencephalon, the preoptic area, the hypothalamus, and the cerebellum (Diotel et al., 2011b). The distributions of *P450scc*, *3 $\beta$ -hsd*, and *cyp17* suggest a potential expression in neurons as well as in neural progenitors, as shown by co-expression with AroB, a RGC marker. From 2011 until now, new isoforms for these steroidogenic enzymes have been identified: *3- $\beta$ hsd1*, *3- $\beta$ hsd2*, *cyp11a1*, *cyp11a2*, *cyp17a1*, and *cyp17a2*. Recent work confirmed the sites of expression of these steroidogenic enzymes in the brain of adult zebrafish and further described the distribution of their respective isoforms (Weger et al., accepted). It appears that all these steroidogenic enzymes display overlapping distributions. In addition, expression of *cyp21a2*, *cyp11c1*, and *fdx1/fdx1b* (co-factors of glucocorticoid synthesis) was recently described in adult zebrafish brain (Weger et al., accepted), and patterns appeared similar to other steroidogenic enzymes. Furthermore, isolation and culture of goldfish RGCs was performed (Xing et al., 2014), and deep RNA sequencing of these RGCs indicates expression of steroidogenic acute regulatory protein (*star*), *cyp11a1*, *cyp17a1*, *fdx1*, *hsd17b10* in addition to *cyp19a1b* and *5 $\alpha$ -reductase* (Da Fonte et al., 2017). Proteomic

analyses also revealed the production of 20 $\beta$ -Hsd (Xing et al., 2016).

Altogether, these studies suggest that the brains of adult fish widely express the biologically active steroidogenic enzymes leading to sex steroid synthesis. They also suggest that RGCs in fish may be capable of *de novo* steroid production from cholesterol and could be consequently envisioned as true steroidogenic cells (Figure 2A).

## Steroidogenic Enzyme Activities and Expression in the Brains of Birds

Birds are excellent models for understanding the impact of peripherally and locally produced steroids on brain functions, including behavior. Pioneering studies from the groups of Tsutsui and Schlinger have shown that the brains of the quail (*Coturnix japonica*) and zebra finch (*Taeniopygia guttata*) are capable of *de novo* steroidogenesis. They showed that the avian brain expresses the active P450<sub>scc</sub>, 3 $\beta$ -HSD, CYP17, 17 $\beta$ -HSD, and aromatase enzymes, leading to the production of a wide variety of neurosteroids including pregnenolone, progesterone, androstenedione, testosterone, and estradiol from cholesterol (Tsutsui and Yamazaki, 1995; Tsutsui et al., 1999, 2006, 2009; Matsunaga et al., 2001; London et al., 2006, 2009; London and Schlinger, 2007; Tsutsui, 2011; Schlinger and Ramage-Healey, 2012). Western-Blot and immunohistochemistry experiments allow the detection of P450<sub>scc</sub> immunoreactive neurons through the preoptic area, the thalamus, the hypothalamus, and the cerebellum in Purkinje cells (Tsutsui, 2011). 3 $\beta$ -HSD expression was highlighted based on enzymatic activity in the brain of the adult quail, with a strong presence in the telencephalon and the diencephalon and a lower one in the mesencephalon (Ukena et al., 1999). In quail, *Cyp17* gene expression is detected in the preoptic area, the thalamus, the hypothalamus, and the optic tectum as well as in Purkinje cells (Matsunaga et al., 2001).

Aromatase expression was thoroughly studied in several brain regions particularly, in the hypothalamus and the preoptic area in quail (Balthazart and Foidart, 1993; Balthazart et al., 1996; Balthazart and Ball, 1998; Tsutsui, 2011) and in the telencephalon in zebra finches (Schlinger, 1997). Interestingly, data showed overlapping distribution of *StAR*, *CYP11A1*, 3 $\beta$ -HSD, and *CYP17* mRNA in the ventricular proliferative zone of the avian brain during support (London and Schlinger, 2007), suggesting potential roles of neurosteroids in neurogenesis and CNS development. It should be noted that 3 $\beta$ -HSD is also present throughout the telencephalon in adult song birds (Soma et al., 2004; Schlinger et al., 2008). Furthermore, aromatase expression was also studied throughout the avian brain during support and *de novo* expression was documented in RGCs following brain injury in adult birds (Peterson et al., 2004). These data surface a potential role of aromatase and estrogen synthesis in neuroprotection and brain repair mechanisms.

These different studies highlight the capacity of the avian brain to synthesize its own steroids and suggest key roles of neurosteroids in reproductive behavior and neurogenesis.

## Steroidogenic Enzyme Activities and Expression in the Brains of Mammals

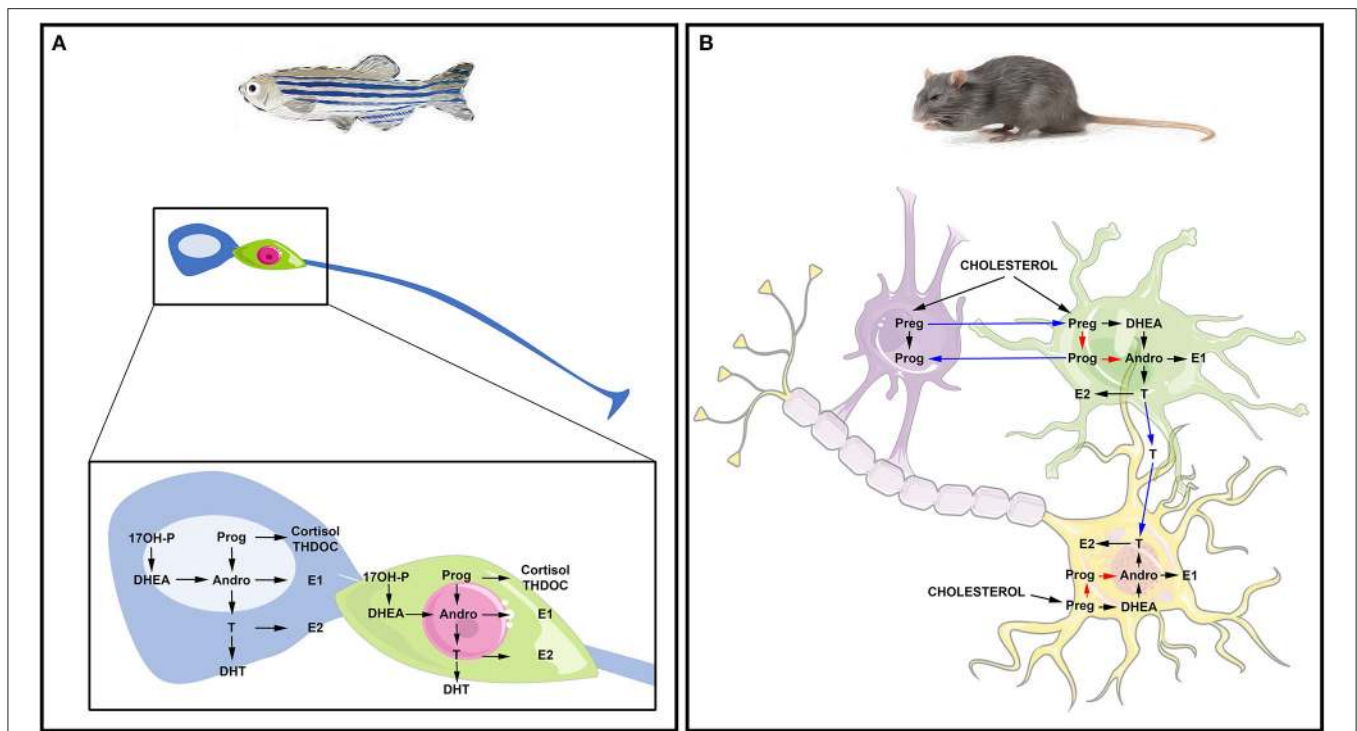
P450<sub>scc</sub> gene expression was detected in numerous brain regions of the rodent (i.e., cerebral cortex) and human brain (i.e., cerebral cortex, olfactory bulbs, hippocampus, cerebellum) (Pelletier, 2010). Cells immunoreactive for P450<sub>scc</sub> were observed in the white matter, the pyramidal and granular neurons of the developing and adult hippocampus (a brain region known for maintaining active neurogenesis during adulthood), and also in Purkinje cells from the cerebellum (Le Goascogne et al., 1987; Tsutsui and Ukena, 1999; Kimoto et al., 2001).

In the 80s, 3 $\beta$ -HSD activity was reported in rat brain homogenates through the conversion of pregnenolone into progesterone (Weidenfeld et al., 1980). More generally, 3 $\beta$ -HSD gene and protein expressions were documented in primary cultures of rodent oligodendrocytes and neurons, and distributed especially in the olfactory bulbs, the thalamus, the cerebral cortex, the hypothalamus, and the cerebellum (Dupont et al., 1994; Guennoun et al., 1995; Meffre et al., 2007; Pelletier, 2010). In humans, 3 $\beta$ -HSD gene expression was detected in neuronal, astroglial, and oligodendrocyte cell lines (Brown et al., 2000) and had a similar distribution compared to rodents, notably in the thalamus, the hippocampus, and the cerebellum (Yu et al., 2002).

The presence of *Cyp17* in the mammalian central nervous system (CNS) is currently not clear. Indeed, some work suggested the absence of *Cyp17* gene expression while other studies reported *Cyp17* gene expression in the cerebellum and the brainstem of rat, and showed *Cyp17* immuno-positive cells in the hippocampus, the hypothalamus, and in the Purkinje cells (Mellon and Deschepper, 1993; Strömstedt and Waterman, 1995; Hojo et al., 2004; Pelletier, 2010). During development, the expression of *Cyp17* in the rat brain is present but decreases postnatally (Compagnone and Mellon, 2000). Hence, the question of *Cyp17* expression and activity in the mammalian brain remains open.

In rodents, aromatase expression (mRNA and protein) and activity were documented in numerous brain regions including the cerebral cortex, the preoptic nucleus, the hypothalamus as well as the hippocampus; in humans, it was also detected in the pons, the thalamus, the hypothalamus, and the hippocampus (Lephart et al., 1992; Lephart, 1996; Sasano et al., 1998; Garcia-Segura et al., 2003; Hojo et al., 2004; Yague et al., 2006; Pelletier, 2010). In rodents, aromatase expression was mainly detected in neurons and not in glial cells, except following brain injury that results in a *de novo* aromatase expression by astrocytes, suggesting a role of estrogens in neuroprotection (Garcia-Segura et al., 1999; Azcoitia et al., 2001; Garcia-Segura, 2008). In contrast to rodents, in some primates including humans, the estrogen-synthesizing enzyme expression was also reported in some subpopulations of astrocytes in addition to neurons (Yague et al., 2006; Roselli, 2007). As reviewed by Pelletier (2010), numerous studies demonstrate aromatase activity in the brain of mammals including primates.

Consequently, *de novo* steroid synthesis occurs in the brains of mammals (Figure 2B). Neurosteroidogenesis is active in



**FIGURE 2 |** Steroidogenesis in the brain of fish and mammals. **(A)** Steroidogenesis in the brain of adult fish. The blue cell corresponds to a radial glia cell acting as neural stem cell, while the green cell corresponds to a neuron. Data obtained by *in situ* hybridization, RNA sequencing and/or proteomics show neuronal and radial glial expression of steroidogenic enzymes involved in the synthesis of 17OH-Pregnenolone (17OH-P), Progesterone (P), dehydroepiandrosterone (DHEA), Androstenedione (Andro), Estrone (E1), 17 $\beta$ -estradiol (17 $\beta$ -E2, called here E2), testosterone (T) and dihydro-testosterone (DHT), cortisol and THDOC (tetrahydrocorticosterone). **(B)** Steroidogenesis in the brain of rat. The purple cell corresponds to an oligodendrocyte that participates in the myelin sheath genesis of axons; the green cell is an astrocyte and the yellow one is a neuron whose axon is myelinated by the oligodendrocyte. This schematic view adapted from Zwain and Yen (1999) highlights potential interaction of oligodendrocytes, astrocytes, and neurons in neurosteroidogenesis. The main steroidogenic pathway is shown by black arrows, the minor ones by red arrows and the suggested ones by blue arrows referring to the work of Zwain and Yen (1999). Note that arrows do not necessarily document the direct conversion of the one steroid into another, but can include several enzymatic processes.

numerous regions including the hippocampus, known for maintaining an intense neurogenic activity during adulthood. Interestingly, this region was shown to synthesize 17 $\beta$ -E2 from pregnenolone (Hojo et al., 2004), reinforcing the idea that steroids could impact neurogenesis.

In conclusion, neurosteroidogenesis appears to be a conserved process well-documented in fish, birds and mammals (Figure 2). It occurs in numerous evolutionary conserved regions such as the telencephalon, the diencephalon (i.e., preoptic area and hypothalamus), and also the cerebellum. This sustained synthesis of steroids may regulate several brain functions and participate to brain homeostasis, neurotransmission, neurogenesis, and brain plasticity by targeting different cell types.

### STEROID SIGNALING IN THE BRAIN: FOCUS ON THE BRAINS OF FISH, BIRDS, AND MAMMALS

Peripherally and locally produced steroids can target different brain regions and cell-types expressing their respective and specific receptors. Here, we will describe the main sites of

expression of steroid receptors, with a special focus on estrogen, progesterone, and androgen receptors. We will first discuss receptor distributions in the brain of fish and birds before highlighting the situation in mammals.

### Expression of Nuclear and Membrane-Associated Steroid Receptors in the Brains of Fish Nuclear Estrogen Receptors (ER)

Unique among vertebrates, fish have three nuclear estrogen receptors resulting from an ancient genome duplication: one ER $\alpha$  and two ER $\beta$ . The ER $\alpha$  and ER $\beta$  probably arose from a first duplication event prior the emergence of ray-finned species. A second duplication led to the emergence of two ER $\beta$  and ER $\alpha$  genes but the second copy of the ER $\alpha$  probably disappeared (Thornton, 2001; Bardet et al., 2002; Nagler et al., 2007).

Nuclear estrogen receptors genes [ER $\alpha$  (*esr1*), ER $\beta1$  (*esr2b*), and ER $\beta2$  (*esr2a*)] were identified in many teleost species, including the rainbow trout (*Oncorhynchus mykiss*), tilapia (*Oreochromis niloticus*), medaka (*Oryzias latipes*), goldfish, and zebrafish among others (Pakdel et al., 1990; Tan et al., 1995;

Muñoz-Cueto et al., 1999; Tchoudakova et al., 1999; Xia et al., 1999; Hawkins et al., 2000; Kawahara et al., 2000; Ma et al., 2000; Socorro et al., 2000; Bardet et al., 2002; Lassiter et al., 2002; Menuet et al., 2002; Andreassen et al., 2003; Choi and Habibi, 2003; Halm et al., 2004; Sabo-Attwood et al., 2004; Filby and Tyler, 2005; Forlano et al., 2005; Nagler et al., 2007; Strobl-Mazzulla et al., 2008; Chakraborty et al., 2011; Zhang et al., 2012; Katsu et al., 2013).

Most studies carried out so far reported the presence of *esr* transcripts in the brain of adult fish. *In situ* hybridization and immunohistochemistry experiments used to localize ER-expressing cells in the brain revealed distinct but partly overlapping patterns of expression in many fish species including medaka, Atlantic croaker (*Micropogonias undulatus*), pejerrey (*Odontesthes argentinensis*), trout and zebrafish (Salbert et al., 1991; Anglade et al., 1994; Hawkins et al., 2000, 2005; Menuet et al., 2002; Pellegrini et al., 2005; Nagler et al., 2007; Strobl-Mazzulla et al., 2008; Zempo et al., 2013; Coumaillau et al., 2015). In general, transcripts for ERs have a broad distribution and were detected in many brain regions known to regulate sexual, reproductive, social behaviors, and sensory-motor activities such as the telencephalon, the preoptic area, the hypothalamus, and the cerebellum. Additionally, ER transcripts have been reported in cells lining the ventricles, where RGCs are localized, and also in cells localized more deeply in the brain parenchyma. Interestingly, there are clear evidences that ER $\alpha$  is expressed in dopaminergic, GABAergic, kisspeptin- and neuropeptide B-positive neurons in several species (Linard et al., 1996; Anglade et al., 1999; Mitani et al., 2010; Escobar et al., 2013; Zempo et al., 2013; Hiraki et al., 2014). Similarly to rodents, ERs were not reported in neurons expressing gonadotrophin-releasing hormone (Navas et al., 1995).

In midshipman (*Porichthys notatus*), pejerrey, and zebrafish, the pattern of expression of the nuclear estrogen receptors and AroB (*Cyp19a1b*) are closely related (Forlano et al., 2005; Strobl-Mazzulla et al., 2008; Diotel et al., 2011a). Careful examination of adjacent sections hybridized with *cyp19a1b* and *esr1* riboprobes in trout and zebrafish failed to evidence any co-localization (Menuet et al., 2003, 2005). However, *esr2b* was recently shown to be expressed in AroB-expressing RGCs (Pellegrini et al., 2015), and RT-PCR analysis performed in glial cells enriched cultures from adult trout or goldfish suggested that a weak expression of ER $\alpha$  could not be excluded (Menuet et al., 2003; Xing et al., 2015). A recent study designed to characterize the transcriptome of cultured goldfish RGCs and reported *esr1*, *esr2b*, and *esr2a* expression in these neural progenitors (Da Fonte et al., 2017).

Knowledge about estrogen signaling during early development in fish is very limited and the zebrafish is the only species in which expression of the three ERs during embryogenesis was monitored. Quantitative-PCR experiments established that *esr1*, *esr2a*, and especially *esr2b* mRNA were maternally inherited and expressed in eggs before dropping down to 24 h post-fertilization (hpf) (Bardet et al., 2002; Lassiter et al., 2002; Mouriec et al., 2009; Bondesson et al., 2015). Nuclear estrogen receptor expression then started to increase at 24 h, when the onset of zygotic transcription is activated (Bardet et al., 2002; Lassiter et al., 2002; Mouriec et al., 2009). Whole mount

*in situ* hybridization showed that *esr2a* and *esr2b* mRNA were detectable at 48 hpf in the ventral telencephalon and in the presumptive preoptic area as well as in the hypothalamus, in line with what was described in the adult brain (Mouriec et al., 2009). A clear expression for *esr1* is described in these regions but at later stages, between 14 days post-fertilization (dpf) and 21 dpf (Kallivretaki et al., 2007; Mouriec et al., 2009). Using *cyp19a1b*-GFP zebrafish embryos, GFP expression was shown to be inducible in RGCs at 24 h after 17 $\beta$ -E2 treatment, an effect blocked by the ER antagonist ICI 182,780, indicating that ERs were fully functional in the brain early during development (Mouriec et al., 2009). A morpholino approach confirmed the specific role of *esr2b* in the induction of the *cyp19a1b* gene (Griffin et al., 2013). Temporary disruption of *esr2a* expression in zebrafish with the same technological approach was associated with a developmental defect of sensory hair cells (Froehlicher et al., 2009). Knockdown of both maternally inherited and zygotic *esr2a* was associated with an increase in apoptotic cells particularly in the brain leading to severe brain defects (Celeghin et al., 2011).

### Membrane-Associated Estrogen Receptors (mER)

Membrane receptors responding to 17 $\beta$ -E2 stimulation via rapid non-genomic signaling have been characterized in fish. G protein-coupled estrogen receptor 1 (GPER or GPR30) is a member of this receptor family. A partial or full-length *gper* was cloned, characterized, and detected in the brain of adult zebrafish, Atlantic croaker, and goldfish (Pang et al., 2008; Liu et al., 2009; Pang and Thomas, 2009; Mangiamele et al., 2017). In zebrafish, *gper in situ* hybridization on adult brain sections showed a specific pattern of expression in the olfactory bulbs, the telencephalon, the hypothalamus, the optic tectum, the cerebellum, and the medulla oblongata (Liu et al., 2009). In goldfish, *gper* was also expressed in the forebrain and the suprachiasmatic nucleus, the preoptic area, and the optic tectum (Mangiamele et al., 2017). Originally, it was proposed that goldfish RGCs did not express the G-protein coupled estrogen receptor because attempts to amplify a specific cDNA from cultured cells failed (Xing et al., 2015). However, whole RNA sequencing of separate primary cultures of these cells revealed expression of *gper1*, suggesting that some subpopulations of RGCs express the membrane ER (Da Fonte et al., 2017).

The spatiotemporal distribution of *gper* was investigated in zebrafish using PCR. Its expression was observed in the anterior diencephalon, the midbrain and the hindbrain (Jayasinghe and Volz, 2012; Shi et al., 2013). Both *gper* and *esr2b* mRNA are expressed in neuromasts, suggesting a role of estrogens and a close interaction between these receptors in the developmental regulation of this mechanoreceptive organ (Froehlicher et al., 2009). Knock-down of *gper* resulted in morphological defects in the zebrafish brain at 24 hpf (Shi et al., 2013). At 30 hpf, these morphants displayed an increased number of apoptotic cells, and a decreased brain cell proliferation (Shi et al., 2013). A slight reduction in *otx2* gene expression, which is required for sensory organs development and brain function, was also observed in *gper* knock-down zebrafish. Taken together, these data show the

potential involvement of both nuclear and membrane-associated estrogen receptors in brain development and functions.

### Nuclear Progesterone Receptors (PR)

Nuclear progesterone receptor (PR) genes have been characterized in a few fish species (Ikeuchi et al., 2002; Morini et al., 2017). In European eel (*Anguilla Anguilla*), two PR genes, *pgr1* and *pgr2*, were differentially expressed in the brain (olfactory bulb, telencephalon, diencephalon, cerebellum) and in the pituitary of immatures males and females (Morini et al., 2017). Two genes were also identified in the Japanese eel (*Anguilla japonica*) but only *pgr2* mRNA was detected in the brain (Ikeuchi et al., 2002). In zebrafish, a single locus encoding PR (*Pgr*) was identified (Chen et al., 2010a; Hanna et al., 2010). Ontogenic expression analysis determined by PCR during early embryogenesis showed that *pgr* mRNA was not maternally inherited and became detectable in embryos at 8 hpf (Chen et al., 2010a). Immunohistochemistry and *in situ* hybridization revealed a widespread distribution of zebrafish Pgr receptor (protein and mRNA) in the brain especially neuroendocrine regions (olfactory bulbs, preoptic area, telencephalon, thalamus, hypothalamus, optic tectum, torus longitudinalis, valvula cerebelli) (Hanna et al., 2010; Diotel et al., 2011c). It should be noted that Pgr-positive cells were observed along the ventricular cavities and also more deeply in the brain parenchyma. In this work, it was shown that periventricular Pgr-positive cells displayed a stronger staining compared to Pgr-positive cells located deeply in the parenchyma (Hanna et al., 2010; Diotel et al., 2011c). By performing double immunostainings, it was shown that a large portion of Pgr-positive cells located in the cerebral parenchyma correspond to acetylated-tubulin positive neurons (Diotel et al., 2011c). In contrast, immunohistochemistry on *cyp19a1b*-GFP transgenic zebrafish clearly showed Pgr-expressing cells along the ventricle correspond to AroB<sup>+</sup> RGCs (Diotel et al., 2011c). These data were confirmed by a transcriptomic analysis showing *pgr* mRNA expression in cultured goldfish RGCs (Da Fonte et al., 2017). Pgr expression is consequently high in the estrogen-synthesizing RGCs. This suggests a relationship between locally-produced estrogens and Pgr expression. Indeed, treatments with the aromatase inhibitor ATD or with 17 $\beta$ -E2 respectively decrease or increase *prg* expression in the brains of adult zebrafish and also in larvae (Diotel et al., 2011c).

Gene knockout using the TALENs strategy allowed to generate zebrafish lines with null Pgr expression to assess the *in vivo* function of this receptor. Unfortunately, all studies performed with these models have focused at the gonadal levels and none of them looked at the effect of Pgr expression disruption in the brain (Zhu et al., 2015; Tang et al., 2016; Wang et al., 2016).

### Membrane-Associated Progesterone Receptors (mPR)

In mammals, many progestins exert non-genomic effects through rapid activation of intracellular signaling pathways mediated by two groups of membrane progesterone receptors: mPRs (belonging to the PARQ family) and PGRMC1 and PGRMC2 (Petersen et al., 2013). However, there are only scarce data on membrane-associated progesterone receptors existence and sites of expression in the brain and the pituitary of fish (Thomas, 2008).

The *mPR $\alpha$*  was identified and detected in the brain of adult spotted seatrout (*Cynoscion nebulosus*) (Zhu et al., 2003). It was also recently cloned in medaka but no data about its brain expression are available (Roy et al., 2017). In goldfish, *mPR $\alpha$* , *mPR $\beta$* , *mPR $\gamma$ 1*, and *mPR $\gamma$ 2* were also detected in the brain (Tokumoto et al., 2006, 2012). Other studies documented the expression of different mPRs and/or PGMRCs in the brain and the pituitary of the European eel (*Anguilla anguilla*), the channel catfish (*Ictalurus punctatus*) and also the rainbow trout (Kazeto et al., 2005; Mourot et al., 2006; Morini et al., 2017). To date, *mPR $\alpha$*  and *mPR $\beta$*  were the only form to be identified in zebrafish (Zhu et al., 2003). Using specific antibodies for zebrafish *mPR $\alpha$*  and *mPR $\beta$* , Hanna and Zhu demonstrated their expression in brain samples (Hanna and Zhu, 2009). Currently, the distributions and functions of mPR in the brain of fish, if any, are completely unknown.

### Nuclear Androgen Receptors (AR)

Two *ar* genes (*ar1* and *ar2*) were isolated and characterized in several fish species including the Japanese eel (*Anguilla japonica*), the rainbow trout, the kelp bass (*Paralabrax clathratus*), the Atlantic croaker, and cichlids (Ikeuchi et al., 1999; Sperry and Thomas, 1999a,b; Takeo and Yamashita, 1999, 2000; Harbott et al., 2007). More recently, only one *ar* isoform was described in the stickleback (Olsson et al., 2005), the wrasse (*Halichoeres trimaculatus*) (Kim et al., 2002), the zebrafish (Jorgensen et al., 2007; de Waal et al., 2008; Gorelick et al., 2008; Hossain et al., 2008), and in the plainfin midshipman (Forlano et al., 2010).

The first immunohistochemistry studies carried out on the brains of adult goldfish with an heterologous antibody revealed AR-positive cells with neuronal appearance in neuroendocrine regions such as the preoptic area and the hypothalamus, as well as in the olfactory bulbs, the telencephalon and the optic tectum (Gelinias and Callard, 1997). More detailed results were obtained in the brain of the plainfin midshipman, a fish that express mating behavior triggered by auditory signal. These data showed mRNA expression in auditory-related nuclei of the telencephalon, hypothalamus, midbrain, and in the vocal prepacemaker and vocal motor nuclei (Forlano et al., 2010). Numerous studies showed AR expression in the brain of fish including among others wrasse and zebrafish (Kim et al., 2002; Harbott et al., 2007; Hossain et al., 2008; Pouso et al., 2010).

In adult zebrafish, *ar* is strongly expressed along the ventricle and within the brain parenchyma of the telencephalon, the preoptic area, and the hypothalamus (Gorelick et al., 2008). In embryos, *ar* transcripts are maternally deposited and expression levels start to increase substantially at 24 hpf (Hossain et al., 2008). The *ar* gene expression is detected at 24 hpf in the olfactory placodes and in the midbrain, at 48 hpf in the medial diencephalon and at 3 dpf in the pineal organ (Gorelick et al., 2008). All neuroanatomical studies undertaken to date show that ARs are expressed in ventricular margins, where RGC are located (Harbott et al., 2007; Gorelick et al., 2008; Forlano et al., 2010; Pouso et al., 2010). Recently, transcriptomic analysis showed the expression of *ar* in goldfish RGCs (Da Fonte et al., 2017).

As mentioned above, it was shown that goldfish RGCs express progesterone receptor (Pgr), androgen receptor (*ar*), estrogen

receptor  $\alpha$  (*esr1*), estrogen receptor  $\beta 1$  (*esr2b*), and estrogen receptor  $\beta 2$  (*esr2a*) (Da Fonte et al., 2017). This data supports other reports in zebrafish showing that RGCs express Pgr protein (Diotel et al., 2011c) and observations for the expression of *ar*, *esr1*, *esr2a*, and *esr2b* mRNAs within neurons and/or AroB<sup>+</sup> RGCs (Diotel et al., 2011a; Pellegrini et al., 2015). All this suggests that RGCs are both a source and a target of neurosteroids (Diotel et al., 2011a; Pellegrini et al., 2015; Xing et al., 2016), arguing for key roles of steroids in RGC activity.

## Expression of Nuclear and Membrane-Associated Steroid Receptors in the Brains of Birds

### Nuclear and Membrane-Associated Estrogen Receptors

Early data on the distribution of sex hormone receptors in the brain of birds was extensively reviewed (Gahr, 2001). Similar to mammals, there are two different avian genes coding for ER $\alpha$  and ER $\beta$  (Bernard et al., 1999; Jacobs et al., 1999). In birds, ER $\alpha$  is expressed in the brain of all the species studied so far, including members of Apodiformes, Passeriformes, Galliformes, Columbiformes, and Psittaciformes. These ERs are distributed in various brain territories including the telencephalon, the diencephalon, and the rhombencephalon, with more noticeable expression in the preoptic area and the hippocampus (Gahr, 2001). For instance, in the brain of zebra finch, ER $\alpha$  mRNAs was observed in the nidopallium, the arcopallium, the hippocampus, the diencephalon, the midbrain and within the vocal control circuitry (Jacobs et al., 1999). Interestingly, ER $\alpha$  mRNAs expression overlap with that of aromatase (Jacobs et al., 1999). ER $\beta$  was first described in the brain of the Japanese quail, the European starling (*Sturnus vulgaris*), and the canary (Bernard et al., 1999; Foidart et al., 1999; Gahr, 2001). In general, ER $\beta$  was reported in the preoptic area, the hypothalamus, the thalamus and different midbrain nuclei. In the European starling, *in situ* hybridization experiments allowed the detection of ER $\beta$  mRNA in the nidopallium and the preoptic area in a pattern reminiscent of aromatase (Bernard et al., 1999; Axelsson et al., 2007). Consequently, ER $\alpha$ , ER $\beta$  and aromatase distributions strongly overlap. As reported in oscine birds, ER labeling was detected in different forebrain regions while it was not found in non-oscine ones, highlighting discrete differences in ER expression in songbird species and families (Gahr, 2001). It should be noted that, while histological studies have focused on the distribution of the nuclear isoforms, numerous functional studies suggest that estrogen receptors act at the level of the membrane, probably via interaction with other receptors such as glutamate receptors (Pawlisch and Remage-Healey, 2015; Seredynski et al., 2015).

### Nuclear and Membrane-Associated Progesterone Receptors

Concerning PR expression, most studies in birds have focused on the hypothalamic region, because of the potential role of PR signaling in reproductive and egg-laying behaviors. Similarly to ER and AR, PR expression was investigated and documented by *in situ* hybridization and immunohistochemistry in the preoptic

area, the hypothalamus, the thalamus, the hippocampus of the zebra finch, and the hen (Sterling et al., 1987; Lubischer and Arnold, 1990).

### Androgen Receptors

The first studies documenting AR distribution in the brain of birds were performed by *in vivo* autoradiography with radio-labeled steroids (Arnold, 1980; Gahr, 2001). In zebra finch, these autoradiographic studies demonstrated the binding of tritiated testosterone in the HVC (used as the proper term, but previously known as hyperstriatum ventrale pars caudalis or and high vocal center), the magnocellular nucleus of the anterior nidopallium, the robust nucleus of the arcopallium, the nucleus intercollicularis of the midbrain, and the periventricular magnocellular nucleus of the anterior hypothalamus (Arnold, 1980). In the golden-collared manakins (*Manacus vitellinus*), *in situ* hybridization for AR revealed expression in the forebrain, in the nucleus taeniae of the amygdala and in the arcopallium (Fusani et al., 2014). In general, ARs are detected in the hypothalamus, the preoptic area, the midbrain, and hindbrain in all species studied to date.

Taken together, it appears that ER, AR, and PR display almost similar distribution in the avian brain, with higher expression in the preoptic area, hypothalamus, thalamus, and hippocampus.

## Expression of Nuclear and Membrane-Associated Steroid Receptor in the Brains of Mammals

### Estrogen Receptors

Data concerning ERs mRNA and protein expression mostly originate from rat studies showing a strong expression of ER $\alpha$  and ER $\beta$  throughout the brain (Li et al., 1997; Shughrue et al., 1997). *In situ* hybridization and immunohistochemistry experiments revealed that ER $\alpha$  and ER $\beta$  are expressed in neurons and glia from many CNS regions including the olfactory bulbs, the preoptic area, the hypothalamus, the zona incerta, the ventral tegmentum as well as the cerebellum in Purkinje cells (Li et al., 1997; Shughrue et al., 1997; Mitra et al., 2003; Frick et al., 2015). Both ERs were also detected in the cerebral cortex and in the hippocampus, with higher ER $\beta$  expression compared to ER $\alpha$  (Shughrue et al., 1997). In the brain of mouse, immunohistochemistry against ER $\beta$  allows the detection of immunoreactive cells in regions similar to the rat. However, ER $\alpha$  expression appears stronger in the hippocampus and the hypothalamus, and lower in the cerebral cortex and cerebellum (Mitra et al., 2003), suggesting some differences in ER signaling between rat and mouse. Importantly, ERs are widely and strongly expressed in the brain of mouse at postnatal day 7, but their respective expression declines the two following days with different kinetics (Sugiyama et al., 2009). In humans, ER $\alpha$  is detected in the cortex at 9 gestational weeks in proliferating zones and in the cortical plate. Its expression subsequently decreases until birth before increasing gain during adulthood. At 15 gestational weeks, ER $\beta$  was also detected in proliferating zones and in the cortical plate with expression persisting in the adult cortex (González et al., 2007). Interestingly, from 15



gestational weeks to adulthood, ER $\alpha$  and ER $\beta$  are detected in the hippocampus including the dentate gyrus, known to be a neurogenic region (González et al., 2007). In the same line, ERs have been detected in embryonic/adult NSCs in rodents and humans, suggesting a roles of estrogen signaling in NSC activity (Brännvall et al., 2002; Kishi et al., 2005; Hajszan et al., 2007; Suzuki et al., 2007; Okada et al., 2010). The spatiotemporally regulated expression of ERs in the embryonic brain of mouse and human, notably in the cerebral cortex and the hippocampus, argue in favor of different roles of estradiol during development (González et al., 2007; Sugiyama et al., 2009). Furthermore, a plasma membrane-associated ER (ER-X, GPER, GPR30, GPER1) was identified in the brain, mediating estrogen activation of MAPK/ERK (Toran-Allerand, 2005). This receptor is functionally distinct from ER $\alpha$  and ER $\beta$  and is up-regulated in the adult brain after ischemic stroke (Toran-Allerand et al., 2002). Its expression in the hippocampus is likely to play a role in synaptic plasticity (Waters et al., 2015).

### Progesterone Receptors

In mammals, progesterone receptors include the classic nuclear PRA and PRB receptors, splice variants, and membrane-associated receptors mPR (mPR $\alpha$ , mPR $\beta$ , and mPR $\gamma$ ) (Brinton et al., 2008). Nuclear PRs are expressed through the brain in neurons and glial cells of the hippocampus, the cortex and the hypothalamus (Hagihara et al., 1992a,b; Brinton et al., 2008), and their expression is up-regulated by estrogens in a region specific manner (Guerra-Araiza et al., 2003). Among the three mPR subtypes described, mPR $\alpha$  is the best characterized pharmacologically. *In situ* hybridization and immunohistochemistry experiments have shown a wide mPR $\alpha$  neuronal expression in the olfactory bulbs, the cortex, the hypothalamus, the hippocampus, and the cerebellum (Meffre et al., 2013). Very interestingly, after traumatic brain injury, mPR $\alpha$  is *de novo* expressed in microglia, astrocytes and oligodendrocytes, highlighting a potential role of this receptor in inflammation and brain repair mechanisms (Meffre et al., 2013). In rat, mPR $\beta$ -expressing neurons are detected in the forebrain and the midbrain (Zuloaga et al., 2012). In human, mPR mRNAs are distributed in the forebrain, the hypothalamus and also the hippocampus (Pang et al., 2013).

### Androgen Receptors

In adult rodents, AR mRNA and protein are detected in neurons and glia of the medial amygdala, the preoptic area, the hypothalamus, the cerebellum, and the dentate gyrus of the hippocampus (Commins and Yahr, 1985; Sar et al., 1990; Hajszan et al., 2007; Feng et al., 2010; Pelletier, 2010; Mhaouty-Kodja, 2017). Interestingly, AR protein level is correlated with circulating levels of estradiol and testosterone across the estrous cycle, suggesting an estrogenic regulation of its expression (Feng et al., 2010).

To conclude, across vertebrate species, the distribution of ER, PR, and AR in the brain are evolutionary conserved, especially in the hypothalamus, the preoptic area, and some striatal regions. They are also expressed in neurogenic brain regions, arguing in

favor of a role sex steroids in the regulation of NSC activity, neuronal differentiation, and cell survival.

## ROLE OF STEROIDS IN THE BRAINS OF FISH, MAMMALS, AND BIRDS

In this third part, we will discuss the action of estrogens, progestagens and androgens on constitutive neurogenesis and their effects on CNS following insults such as stroke and traumatic brain injury, with a focus on the impact of sex on brain injury. Then, we will discuss the impact of neurosteroids on behavior in fish, birds, and rodents, focusing only on sexual behavior.

### Constitutive and Regenerative Neurogenesis

The actions of steroids in the brain are complex and depend of many factors such as the strain, the species, the timing, the concentration, and the rhythm of secretion, as well as the regions studied (Duarte-Guterman et al., 2015; Heberden, 2017). Sex steroids are well-documented for impacting neuronal plasticity including synaptogenesis/spinogenesis such as shown for estrogens (Fester et al., 2012; Brandt et al., 2013; Sellers et al., 2015; Sager et al., 2017), progesterone (Sakamoto et al., 2001b, 2002; Zhao et al., 2011), and testosterone (Manolides and Baloyannis, 1984; Devoogd et al., 1985). They have been also well-characterized for their role on learning/memory processes (Frye and Walf, 2008, 2010; Frye et al., 2008; Phan et al., 2012; Celec et al., 2015; Frick et al., 2015). In addition, estrogens, progestins, and androgens display neuroprotective effects through genomic and non-genomic mechanisms (López-Rodríguez et al., 2015). These neuroprotective effects involved the upregulation of anti-apoptotic factors (i.e., Bcl2) and antioxidant enzymes (i.e., SOD and GPx), as well as the down-regulation of pro-inflammatory cytokines (López-Rodríguez et al., 2015). Due to limited space and to avoid redundancy with recently published reviews (Shahrokhi et al., 2012; Heberden, 2017; McEwen and Milner, 2017), we will mainly focus on the roles of these sex steroids on neurogenesis under homeostatic and regenerative conditions (i.e., stroke, traumatic brain injury).

### Effects of Estrogens

In the brain, estrogens modulate synaptic plasticity, NSC proliferation, newborn neuron migration, differentiation, and survival, as well as neuroprotection (McEwen and Woolley, 1994; McEwen et al., 1995; Azcoitia et al., 2001; McCullough et al., 2003; Murashov et al., 2004; Mukai et al., 2010; Frick et al., 2015).

For instance, 17 $\beta$ -E2 treatment of rat embryonic NSCs increases cell proliferation and neuronal differentiation (Brännvall et al., 2002), and promotes human embryonic NSC differentiation into dopaminergic neurons (Kishi et al., 2005). In addition, ER $\beta$  knock-out mice display a thinner cortex at E18.5 due to defects in neuronal migration and increased cell-death arguing for a role of ER $\beta$  in newborn neuronal differentiation and survival during the late phase of corticogenesis (Wang et al., 2003).

During adulthood, rat hippocampal cell genesis in female is modulated by ovarian hormone levels and is higher during pro-estrus, when 17 $\beta$ -E2 concentration is elevated (Tanapat et al., 1999, 2005). In the same line of evidence, ovariectomy leads to decreased hippocampal proliferation that is restored by 17 $\beta$ -E2 treatments through ER dependent mechanism as demonstrated by the use of specific ER agonists (Mazzucco et al., 2006). The impact of other estrogens such as estradiol-benzoate, 17 $\alpha$ -E2, and estrone have been shown to also increase cell proliferation in ovariectomized rats suggesting that the positive neurogenic effects of estrogens are a general feature of female sex hormones (Frick et al., 2015). In meadow voles (*Microtus pennsylvanicus*), the reproductive status also influences dentate gyrus cell proliferation and/or surviving (higher in inactive females; higher in active males) (Ormerod and Galea, 2001, 2003). However, hippocampal cell proliferation in squirrels (*Sciurus carolinensis*) was not shown to be sexually dimorphic and to be modulated across the reproductive cycle (Lavenex et al., 2000). Furthermore, in striking contrast with most studies, an acute 17 $\beta$ -E2 treatment decreases cell proliferation in the subventricular zone (SVZ) and leads to a decrease in newborn cells in the olfactory bulbs (Brock et al., 2010). In addition, chronic 17 $\beta$ -E2 treatments in zebrafish impair NSC proliferation, cell survival, and the newborn cell migration (Diotel et al., 2013).

Estrogens also display neuroprotective properties and promote neural regeneration following traumatic brain injury and cerebral ischemia by decreasing apoptotic signaling, neuroinflammation, and oxidatative stress and by normalizing glutamate concentrations (Petrone et al., 2015). These neuroprotective effects of estrogens on brain ischemia have been well-established in ovariectomized rodents, and result in a significant decrease in the size of the lesion and in the infarct volume (Gibson et al., 2006; Petrone et al., 2015).

### Effects of Progesterone and Allopregnenolone

In the brain, progesterone is known to regulate spinogenesis, synaptogenesis, neuronal survival, and dendritic growth (McEwen and Woolley, 1994; Brinton et al., 2008; Tsutsui, 2008; Zhang et al., 2010; Rossetti et al., 2016). Following cerebral ischemia in rat, progesterone promotes neurogenesis in the SVZ of the lateral ventricles and favors cell survival in the peri-infarct region several days post-stroke (Jiang et al., 2016). Interestingly, numerous studies documented estrogen and progesterone effects on learning and memory across the estrous cycle as reviewed in Duarte-Guterman et al. (2015). Allopregnanolone, a progesterone metabolite considered as one of the most important neuroactive steroid in the CNS, also plays key roles by increasing neurogenesis, neuronal cell survival, and by reducing cell-death in the hippocampus and the midbrain (Charalampopoulos et al., 2008; Zhang et al., 2015; Rossetti et al., 2016). It also exerts major neuroprotective roles in neurodegenerative diseases (Rossetti et al., 2016).

### Effects of Androgens

Concerning androgens, a pioneer study in songbird suggested that testosterone could favor neurogenesis (Louissaint et al., 2002), further corroborated by mice castration studies resulting

in decreased hippocampal neurogenesis (Spritzer and Galea, 2007; Heberden, 2017). In songbirds, androgens and estrogens are well-known to induce seasonal-like growth of song nuclei in the adult (Tramontin et al., 2003; Balthazart and Ball, 2016). Additional experiments in rodents document the positive effect of testosterone on SVZ cell proliferation (Tramontin et al., 2003; Farinetti et al., 2015; Balthazart and Ball, 2016), and those of testosterone and dihydrotestosterone on newborn neuron survival (Spritzer and Galea, 2007). In the same line, testosterone increases neurogenesis in wild-type males but not in androgen-insensitive ones (Hamson et al., 2013). This effect is blocked by AR antagonist (flutamide), demonstrating that androgens act through AR and not through ER after conversion into estrogens (Hamson et al., 2013). However, the reality appears more complex as treatment with nandrolone, a synthetic androgen, decreases hippocampal neurogenesis in male and female (Brännvall et al., 2005). Experiments performed in post-ischemic mice established that endogenous androgens do not alter injury-induced neurogenesis, while supra-physiological levels of testosterone and dihydrotestosterone strongly inhibits post-stroke neurogenesis in the dentate gyrus, reducing brain repair (Zhang et al., 2014).

### Sex Difference after Brain Injuries

Interestingly, clinical and experimental findings are abundant and highlight important sex differences after stroke (Roof and Hall, 2000; Girijala et al., 2017). Clinical studies showed that aging women display worse outcomes following ischemic stroke than men, and higher mortality after hemorrhagic stroke (Sohrabji, 2015). In addition, ischemic stroke model in rodents document that young female have smaller infarcted area than young males (Alkayed et al., 1998), and also exhibit less severe stroke consequences during pro-estrus (high 17 $\beta$ -E2 concentration) than during metestrus (low 17 $\beta$ -E2 concentration) (Liao et al., 2001). However, these studies only correlate between levels of 17 $\beta$ -E2 and stroke severity without taking into consideration other steroid hormone such as progesterone. During aging, mortality is higher in female than in male, and in the case of hemorrhagic stroke, males display greater bleeding and mortality (Sohrabji, 2015). It was also shown that estrogen treatments improve outcomes in young females and males after ischemic and hemorrhagic stroke, while their effects are controversial on aging females during ischemia (Sohrabji, 2015). Other clinical and experimental findings also document the impact of gender and of sex steroids on other CNS insults. For instance, after traumatic brain injury, men displayed greater levels of injury severity as indicated by the Glasgow Coma Scale score, but such an effect is not always found (Slewa-Younan et al., 2004; Davis et al., 2006). Taken together, these data argue in favor of an impact of sex and circulating steroids on the consequences of CNS insults.

In conclusion, sex steroids, peripherally or centrally produced, exert numerous actions on constitutive and regenerative neurogenesis, on brain plasticity, learning, and behaviors (**Figure 3**). For more details on sex hormone modulation of hippocampal neurogenesis, see (Galea et al., 2006; Frick et al., 2015).

## Sexual Behavior

As introduced earlier, sex steroids modulate in a wide array of behaviors, including aggression, parental behavior, sexual behavior, but also more cognitive aspects, including attention and visual and verbal memory. Although original studies investigated the role of gonadally-produced steroids, it is now clear that the local synthesis of these steroids directly in the central nervous system play a significant role as well. The shift from systemic to local synthesis and regulation of steroid action within target tissues, such as the brain, was called “Balkanization” of the endocrine system (Schmidt et al., 2008). This process would allow the brain to produce specific steroids required for the activation of defined behavior, while leaving other tissues unaffected. The central synthesis of estrogens in the male brain is probably the best example, as high peripheral production of these steroids would have major feminizing effects. Amongst the many behavioral effects of steroids, we chose to discuss in more detail the steroid-dependent modulation of sexual behavior. Indeed, the neuroanatomy and physiology underlying this reproductive behavior have been under study for decades, and sexual behavior provide an excellent model to further investigate the respective role of locally- vs. peripherally- produced sex steroids.

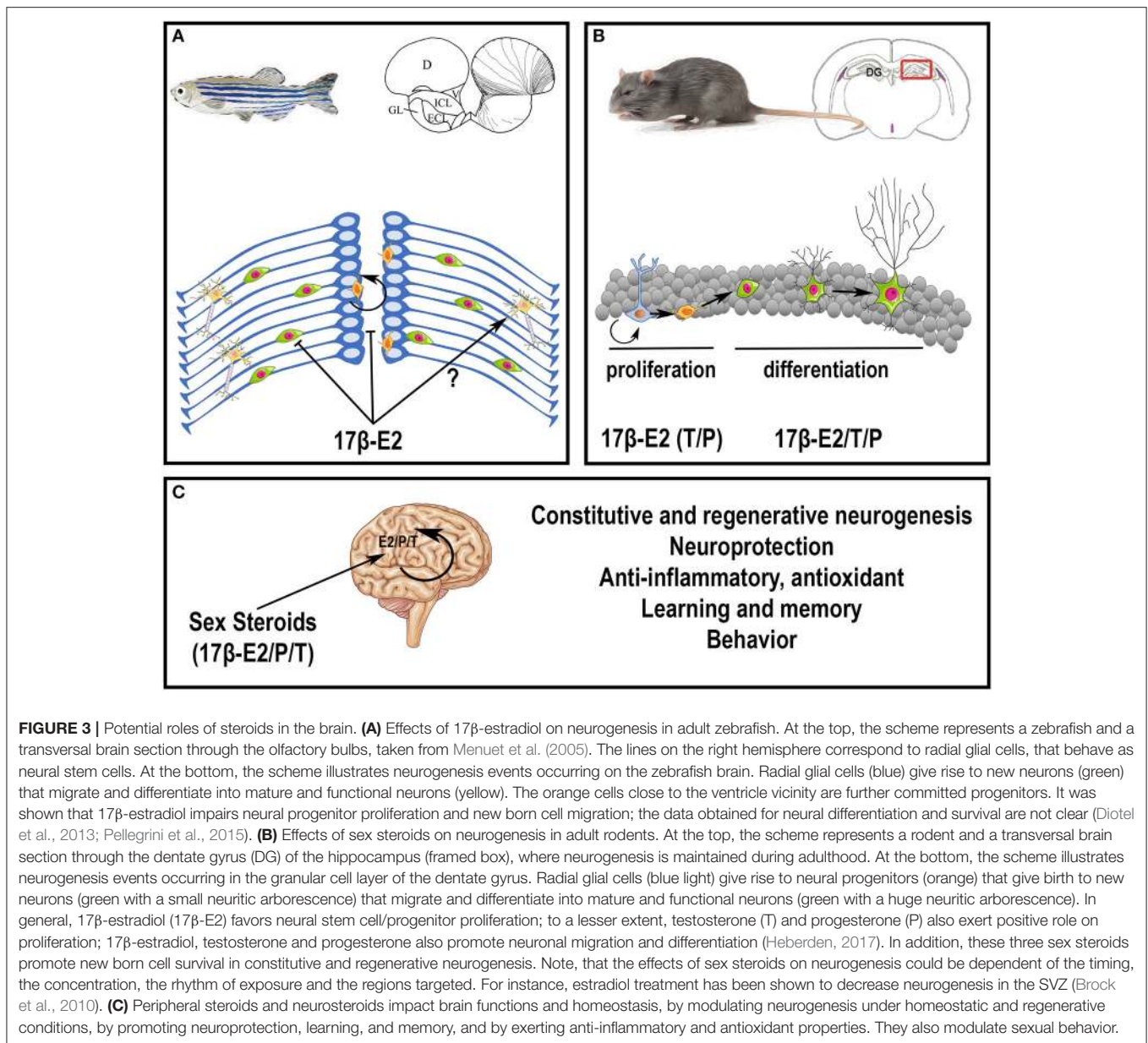
### Importance of Neuroestrogens

The role for aromatase on male sexual behavior was hypothesized over 50 years ago (Clemens, 2013; Södersten, 2013) and a very large number of studies using pharmacological tools have demonstrated that testosterone action on male sexual behavior in various species requires its aromatization in the brain (Christensen and Clemens, 1975; Beyer et al., 1976; Morali et al., 1977; Balthazart and Foidart, 1993; Roselli et al., 2003). These observations were further confirmed by the use of various aromatase knock-out mice (Fisher et al., 1998; Honda et al., 1998; Matsumoto et al., 2003; Bakker et al., 2004). Furthermore, the importance of the central production of estrogens was highlighted by stereotaxic experiments affecting estrogen synthesis within the preoptic area. This region is a key brain center involved in the control of male sexual behavior in most vertebrate species and, importantly, contains a very high concentration of aromatase, especially in birds (Balthazart et al., 2004; Perkins and Roselli, 2007; McCarthy, 2011). Numerous studies have shown that preoptic aromatase activity is critical for the activation of male sexual differentiation and male sexual behavior. For example, chronic inhibition of aromatase activity by specific inhibitors delivered to the preoptic area results in the complete suppression of copulatory behavior within a few days (Christensen and Clemens, 1975; Watson and Adkins-Regan, 1989a; Balthazart and Surlemont, 1990; Balthazart et al., 1990). In castrates, the male sexual behavior can be restored by the local administration of testosterone as well as estrogens (Christensen and Clemens, 1974; Watson and Adkins-Regan, 1989b). These results indicate that the expression of male sexual behavior is tied to changes in aromatase concentration and activity in the preoptic area (POA). Interestingly, these changes in aromatase expression and male sexual behavior are also linked to an important local neuroplasticity (Aste et al., 1993; Panzica et al., 1998; Charlier et al., 2008). It should be noted that most of these

effects were taking place after several days of steroid treatment, clearly suggesting direct genomic effects via the activation of nuclear receptors (Panzica et al., 1998; Scordalakes et al., 2002; Balthazart et al., 2004).

In addition to the long-term effects of estrogens, estrogens also display rapid effects on several aspects of male sexual behavior. For example, research in mouse and Japanese quail showed that acute modulation of estrogen concentrations rapidly affect male sexual behavior (Cornil et al., 2006; Taziaux et al., 2007; Seredynski et al., 2013, 2015). Many of these rapid effects require doses of estradiol that surpass systemic estradiol concentrations in the blood, but local estradiol levels could reach high concentrations quickly, because aromatase and other steroidogenic enzymes can be rapidly regulated in the brain (see below) and are enriched in subcellular compartments such as the presynaptic bouton (Peterson et al., 2005; Saldanha et al., 2011; Cornil et al., 2012). These rapid and local effects of steroids have led to the hypothesis that neuroestrogens act as neurotransmitters (Balthazart and Ball, 2006). Moreover, exposure to sexual stimuli will in turn affect aromatase activity in several regions. Indeed, copulation rapidly and significantly reduced aromatase activity in hypothalamic nuclei and in median preoptic nucleus or tuberal hypothalamus isolated using the Palkovits punch technique (Cornil et al., 2005; de Bournonville et al., 2013). Conversely, exposure to stress upregulates aromatase activity within 5 min in a sex- and brain region-dependent manner in quail (Dickens et al., 2011, 2013), but this increase was counteracted by copulation with a female (Dickens et al., 2012). The mechanisms leading to rapid changes of aromatase activity seem to rely on phosphorylation-dephosphorylation processes but the exact mechanisms are far from being understood (Balthazart et al., 2005, 2006; Charlier et al., 2011a).

It should be noted that the measurements of estrogens do not correlate with aromatase activity in most cases and future work should tackle this discrepancy (Charlier et al., 2011b; Dickens et al., 2014; de Bournonville et al., 2017b). Interestingly, central aromatase is not only important for male sexual behavior but was also shown recently to be involved in female sexual behavior in Japanese quail (de Bournonville et al., 2016, 2017a), see also recent discussion in Cornil (2017). The very high concentration of aromatase in birds make them a very suitable model to investigate its function in modulating sexual behavior but it is likely that rapid change in aromatase activity are also important in mammals and fish, as rapid effects of estrogens were demonstrated on sexual motivation in rat and Goldfish (Cross and Roselli, 1999). However, little is known about the behavioral role of aromatase in fish. As stated above, fish in general possess a very wide distribution of aromatase but the presence of high levels of aromatase, androgen, and estrogen receptors, in brain regions involved in the detection and processing of visual stimuli, suggests that visual processes related to reproduction may be influenced by sex steroids (Gelinas and Callard, 1993, 1997). Testosterone is necessary and sufficient for the enhancement of male approach responses toward a female stimulus to occur and androgen treatments in female goldfish also induce selective approach responses toward female visual stimuli (Thompson et al., 2004). Injections of 17 $\beta$ -E2 had the same behavioral effect



as testosterone, and pretreatment with the aromatase inhibitor (fadrozole) 15 min prior to testosterone injections significantly reduced the male's ability to detect and/or orient toward potential mates. Local  $17\beta$ -E2 synthesis in neural pathways involved in visual processing could therefore sensitize the males to some visual features of females and modulate orientation responses in the context of reproduction (Lord et al., 2009).

### Importance of Neuroprogestins: Neuroprogesterone

In most species, the synchrony between ovulation and female sexual behavior is obviously fundamental for efficient reproductive output. Both processes require a sequential elevation of estradiol and progesterone (Mahesh and Brann, 1998; Stephens et al., 2015). Although preliminary observations

suggested that progesterone originating from the periphery (Buckingham et al., 1978; Putnam et al., 1991; Mahesh and Brann, 1992), ovariectomized and adrenalectomized rats continue to produce a LH surge in response to estradiol priming, suggesting a role for the central production of progesterone (Ferin et al., 1969; Micevych et al., 2003). This central production of neuroprogesterone is linked to astrocytic activity as astrocytes possess transport proteins (TSPO, StAR) and steroidogenic enzymes (P450ssc,  $3\beta$ HSD, etc.) required to transform cholesterol into progesterone. Importantly, the synthesis of progesterone in female hypothalamic astrocytes is regulated by estradiol. This estradiol, from gonadal origin will likely affect the transcription and/or activity of multiple transporters and enzymes, including StAR, TSPO, P450ssc,

and  $3\beta$ -HSD, as observed *in vitro* and *in vivo* (Sinchak et al., 2003; Soma et al., 2005; Micevych et al., 2007; Micevych and Sinchak, 2008a; Kuo et al., 2010; Chen et al., 2014). To our knowledge, the role of neuroprogesterone on the display of sexual behavior is currently not known, although the very fast effect of progesterone receptor antisense oligonucleotides on lordosis behavior could suggest a local synthesis of progesterone (Mani et al., 1994). Although the role of neuroprogesterone on female sexual behavior has not been extensively studied, the function of its metabolite allopregnanolone has been investigated in more detail (Frye, 2011).

### Importance of Neuroprogestins: Allopregnanolone

Allopregnanolone, also known as  $3\alpha$ -hydroxy- $5\alpha$ -pregnan-20-one ( $3\alpha,5\alpha$ -THP), is a neurosteroid produced in several regions of the central nervous system by local conversion of progesterone via  $5\alpha$ -reductase. After paced mating  $3\alpha,5\alpha$ -THP rapidly increases in the midbrain ventral tegmental area (VTA), a dopaminergic region involved in reproductive behaviors of female rodents. The rapidity of the rise in midbrain  $3\alpha,5\alpha$ -THP levels, and independence of ovaries and/or adrenals as sources of steroids, suggest that biosynthesis underlies mating-induced increases (Frye and Vongher, 1999). Paced mating also increases  $3\alpha,5\alpha$ -THP concentrations in other structures of the mesocorticolimbic circuit, such as hippocampus, and cortex (Frye et al., 2013). Central infusions with an inhibitor of TSPO (PK-11195), or with an inhibitor of  $3\alpha$ -HSD within the midbrain VTA significantly attenuated  $3\alpha,5\alpha$ -THP levels of pro-estrus rats and led to a significant reduction in sexual behavior (Frye and Paris, 2011). In order to assess whether central  $3\alpha,5\alpha$ -THP is necessary and sufficient for these effects, pro-estrus rats were infused with  $3\alpha,5\alpha$ -THP subsequent to inhibitor infusions and results indicated a reinstatement of sexual behavior (Frye and Paris, 2011). In hamsters, infusions of a TSPO agonist, to the VTA increased sexual responsiveness and lordosis of cycling, estradiol and progesterone-primed hamsters, compared to vehicle. In contrast, and similarly to what was observed in rat, the TSPO antagonist (PK-11195) injection to the VTA attenuated sexual responsiveness of naturally receptive or estradiol benzoate (EB) + progesterone-primed hamsters compared to vehicle. In parallel, these treatments respectively led to increased and decreased midbrain levels of allopregnanolone (Petralia and Frye, 2005). Future work should define in more detail the precise relationship between localized allopregnanolone synthesis and specific sexual behaviors.

Neurosteroid synthesis is pronounced during early development. Numerous steroidogenic enzymes are expressed at very high levels in the developing avian brain (Goodson et al., 2005; Tsutsui et al., 2006; London and Schlinger, 2007). In rodent brain, most steroidogenic enzymes are typically expressed at much lower levels compared to fish and birds and thus more difficult to quantify but the developmental expression pattern was described for a few steroidogenic enzymes. For example, in rats, brain expression of P450c17, the enzyme responsible for the transformation of pregnenolone to DHEA, is elevated in the embryo and decreases postnatally (Compagnone and Mellon, 2000). Brain  $3\beta$ -HSD mRNA in rodents is highest

during early development (Ibanez et al., 2003). Although steroids from gonadal origin are known to be a significant parameter in sex differentiation in bird, neurosteroids may regulate sexual differentiation in songbird species. In nestling European starlings, neural metabolism of DHEA and  $17\beta$ -E2 can be greater in males than females at specific ages (Chin et al., 2008; Shah et al., 2011). In zebra finches,  $17\beta$ -E2 synthesized *de novo* in cultured male brain slices triggers development of an important projection in the song control circuit (Holloway and Clayton, 2001). Female brain slices developed this projection only when co-cultured with male slices, suggesting a sex difference in neural  $17\beta$ -E2 synthesis during development (Holloway and Clayton, 2001; Schlinger et al., 2001). Progesterone is also synthesized in the brain during development (Zwain and Yen, 1999; Micevych and Sinchak, 2008a,b) and promotes myelination (Koenig et al., 1995; Schumacher et al., 2007).

## STEROIDS AND LIPOPROTEINS: FROM PERIPHERY TO THE BRAIN

### Transport and Actions of Steroids on the Blood-Brain Barrier

Although neurosteroids play key roles on brain functions, peripheral steroid hormones have the main effects on the CNS, either by crossing the BBB or by targeting the BBB cells, which in turn impact the brain parenchyma by modulating inflammatory and oxidative signals. Some of these possibilities were recently discussed in a review for other hormones called adipokines (Parimisetty et al., 2016). In this part, we will first describe the structure of the BBB in fish, birds, and mammals, then document the transport of steroid through the BBB before discussing the potential roles of steroids on the BBB.

### Blood-Brain Barrier in Fish, Bird, and Mammals

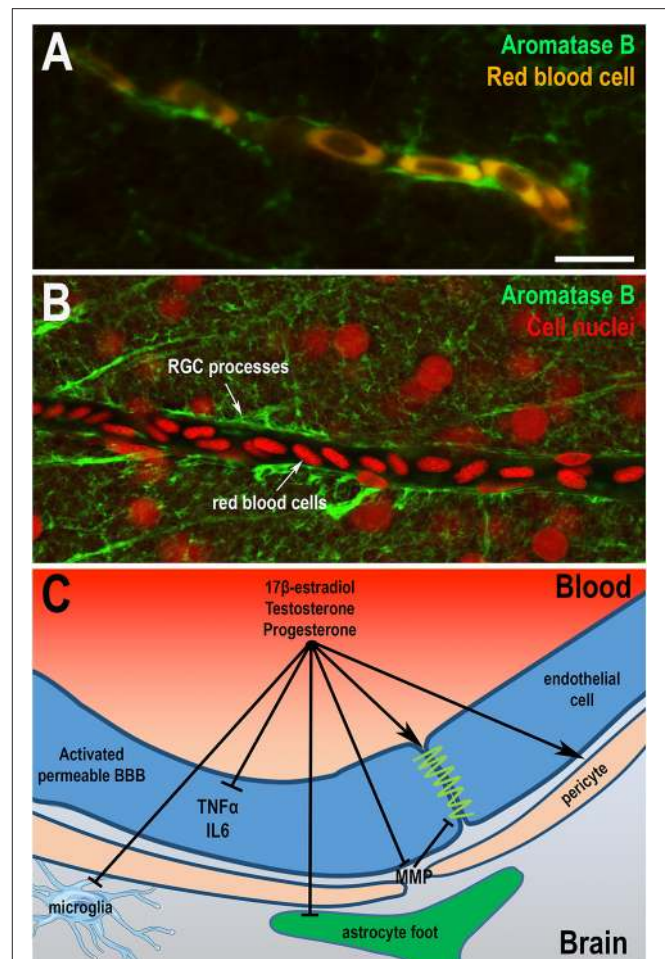
The BBB is a specialized layer of cells that controls molecular trafficking between blood and brain, and contributes to the regulation (homeostasis) of the brain microenvironment. In mammalian species, BBB is composed of adjacent endothelial cells bound to each other by tight junctions whose major components are transmembrane and cytoplasmic anchoring protein such as occludin, claudin, and zona occludens (ZO-1). To complete the barrier, endothelial cells are wrapped by pericytes and surrounded by astrocytic cytoplasmic processes called end-feet. This cellular association is important for proper brain homeostasis, neuronal activity but also for protecting nervous tissue pathogens and harmful molecules transported by blood flow. The BBB, by separating the peripheral blood circulation from the brain parenchyma, filters the entrance of many molecules but also the removal of molecules from the brain (Banks, 2012).

Very few studies have focused on anatomical and functional organization of the BBB in birds and fish. Electron microscopy performed in adult and embryonic brains of quail and chicken showed that cerebral endothelial cells of both species are bound by tight junctions and that BBB is probably functional very early during embryonic development (Wakai and Hirokawa, 1978;

Stewart and Wiley, 1981; Roncali et al., 1986). In embryonic chick, aquaporin 4, a molecular water channels identified in mammalian BBB, was described in astroglia (Nico et al., 2001). In zebrafish, anatomical analysis and transmission electron microscopy revealed that adult endothelial cells display physical barrier properties and express Claudin-5 and ZO-1 proteins (Jeong et al., 2008; Eliceiri et al., 2011; Li et al., 2017). Complete maturation of the zebrafish BBB occurs between 3 and 10 days when expression of Claudin-5 and ZO-1 proteins are detected in cerebral endothelial vascular cells (Jeong et al., 2008; Eliceiri et al., 2011; Fleming et al., 2013; Li et al., 2017). Although some studies have highlighted the presence of stellate astrocytes in some fish (Kawai et al., 2001; Alunni et al., 2005; Strobl-Mazzulla et al., 2010), immunohistochemistry against GFAP or S100 $\beta$  protein has generally failed to demonstrate the presence of star-shaped cells resembling mammalian astrocytes in brain of many fish, including trout, carp, and zebrafish (Arochena et al., 2004; Pellegrini et al., 2005; Grupp et al., 2010; März et al., 2010). These findings raise the possibility that specialized functions of mammalian astrocytes could be supported by the GFAP, BLBP, and S100 $\beta$ -positive RGCs that remains numerous in adults. RNA sequencing analysis performed on goldfish RGC revealed the presence of many receptors and signaling molecules known to be expressed by astrocytes in mammals, a finding that strongly suggests that RGCs share functional similarities with mammalian astrocytes (Grupp et al., 2010; Fleming et al., 2013; Da Fonte et al., 2017). Very interestingly, in the zebrafish brain, blood vessels are wrapped by AroB<sup>+</sup> processes, in a way similar to astrocytic end-feet in mammals, further reinforcing the idea that RGCs in fish perform some, if not all, functions of astrocytes (Figures 4A,B).

### Steroid Transport through the Blood-Brain Barrier

Steroid hormones are lipophilic and thus may cross the BBB by simple diffusion (Witt and Sandoval, 2014). Hormones can also enter the brain via specific transporters (Banks, 2012). In mammals, the transporters that help the passage from the blood circulation to the brain parenchyma are named influx transporters and include organic anion transporting polypeptides (OATPs), proton-coupled monocarboxylate transporters (MCTs), and peptide transporter. In the case of simple diffusion through the BBB, steroid concentrations will tend to equilibrate between the plasma and the brain. However, most steroid hormones are transported in the blood by albumin, sex hormone-binding globulin, or by corticosteroid-binding globulin, changing their availability and the possibility of passive diffusion through the BBB, as shown in most vertebrates, including fish, birds, and mammals (Hammond, 2011, 2016; Rosner, 2015). In rats, radiolabeled steroids (i.e., progesterone, testosterone, estradiol and corticosterone, and cortisol), intravenously injected have been shown to diffuse through the BBB, but this diffusion was significantly slowed down by the presence of binding globulin (Pardridge and Mietus, 1979). In addition, one must take into account that the concentration of carrier proteins may be different in the peripheral circulation vs. the cerebrospinal fluid (CSF). For example, the albumin concentration is one hundred time less important in the CSF



**FIGURE 4 |** Sex hormones restore blood-brain barrier physiology and integrity. (A,B) Aromatase B immunohistochemistry (green) on zebrafish brain highlights that radial glial processes envelop blood vessels as shown by the auto-fluorescence of red blood cells (A) or by nuclear staining (B). These data suggest that radial glial cells could endorse the role of astrocytes in the establishment of the BBB, given the absence of astrocytic cell-type in the brain of fish. It also raises the question of the potential role of locally-produced estrogens on the BBB physiology. Scale bar: 7  $\mu$ m. (C) Sex steroids (17 $\beta$ -E2, progesterone, and testosterone) display direct and indirect effects on the BBB through the restauration of tight junctions, the inhibition of inflammatory cytokine expression and metalloproteinases production, the regulation of pericytes contraction, and consequently the modulation of cerebral blood flow. They also limit reactive gliosis through the inhibition of glial activation under pathological conditions (astrocytes and microglia). Sex steroids participate in the maintenance of a functional BBB, reducing neuroinflammation and promoting neuroprotection.

than in the plasma in humans (Alafuzoff et al., 1983), potentially modulating availability and stability of the steroids.

In addition, hormones may be transported back into the blood circulation by efflux transporters. In mammals, these transporters, belonging to the ABC (ATP Binding Cassette) family, play a key role in brain homeostasis and mediate active efflux of many potential toxicants including lipophilic compounds. They include the P-glycoprotein, also known as

MDR1, ABCB1), multidrug resistance-associated protein, and breast cancer-related protein (Witt and Sandoval, 2014). Organic ion transporting polypeptides (OATPs) and the organic ion transporters, which belong to the solute-linked carrier (SLC) class, could be involved in uptake and/or efflux (Kusuhara and Sugiyama, 2005). For example, metabolites of estrogens can be transported back in the blood circulation from the brain such as demonstrated in male rats (Sugiyama et al., 2001). The same was also shown in rats for the neuroactive androgenic steroid dehydroepiandrosterone sulfate (DHEAS) that is transported back through a member of the SLC class (Asaba et al., 2000). However, the role of efflux transporter in the regulation of the concentration of steroids in the brain is not well-known and remains controversial.

### Effects of Steroids on the Blood-Brain Barrier

Steroids could act directly or indirectly on the BBB, notably by binding to receptors present in the cells composing the BBB. The effects of glucocorticoids on the BBB are well-described and notably include decrease in inflammation (cytokines, chemokines, metalloproteinases) and increase in protective or reparative effects on tight junctions (Witt and Sandoval, 2014). Sex steroids were also shown to exert protective effects on the BBB, using microvessel endothelial bEnd.3 cells (Na et al., 2015). Considering estrogens, treatment with  $17\beta$ -E2 restores the BBB integrity and its permeability in a model of stroke or in a lipopolysaccharides-induced inflammation in rodents (Maggioli et al., 2016; Xiao et al., 2017). Of interest, the BBB permeability is increased when circulating estrogens decrease with aging (Bake and Sohrabji, 2004). With respect to androgens, when gonadal testosterone is depleted from the body, glial cells (microglia and astrocytes) are activated and BBB permeability and inflammation are increased. Testosterone treatments restore these parameters (Atallah et al., 2017). Finally, it also seems that progesterone exerts positive effects on the BBB physiology after stroke and TBI (Ishrat et al., 2010; Si et al., 2014). The effects (direct and indirect) of steroids on the BBB is described in **Figure 4C**.

Interestingly, it was also demonstrated that sex steroids ( $17\beta$ -E2, testosterone, and progesterone) regulate both cerebrovascular tone, endothelial function, oxidative stress, and inflammation as well as brain functions under normal and/or pathological conditions (i.e., middle cerebral artery occlusion: MCAO) (Krause et al., 2011; Gonzales, 2013; Si et al., 2014).

### Lipoproteins in the Brain

Lipid metabolism, high density lipoprotein (HDL)-, and low density lipoprotein (LDL)-cholesterol were studied in a wide variety of groups including rodents, lagomorph, birds, and fish (Liu and Wu, 2004). Lipoprotein metabolism, HDL-, and LDL-cholesterol in zebrafish appear similar to humans, making zebrafish an appropriate model for studying lipoproteins, given that zebrafish express the main set of lipid transporters, apolipoproteins, and enzymes involved in lipoprotein metabolism (Fang et al., 2014). However, to our knowledge, except in rodents, not much is known concerning the effects of HDL-cholesterol in the transport of steroids, in the

maintenance of the BBB integrity and in neuroprotection. We consequently emphasize these points in this last part.

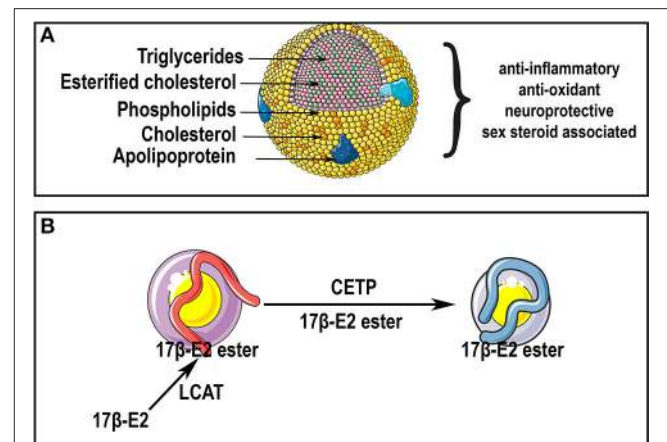
The brain is a cholesterol-rich organ, accounting for about 25% of the total amount present in humans. In the CNS, cholesterol is mainly synthesized by astrocytes, oligodendrocytes, microglia and to a lesser extent by neurons, where it is essentially present in its unesterified form (Björkhem and Meaney, 2004; Dietschy and Turley, 2004; Zhang and Liu, 2015). Brain cholesterol is involved in myelin sheath genesis, in synaptogenesis, and neurotransmission as well as in neurosteroidogenesis (Mauch et al., 2001; Do Rego et al., 2009; Linetti et al., 2010; Liu et al., 2010; Zhang and Liu, 2015). In adults, sterols are excreted from the brain to the plasma, and cholesterol is converted into 24S-hydroxycholesterol, which is more soluble and may diffuse across the BBB to reach the plasma where it is metabolized to bile acids after being picked up by circulating lipoproteins (Quan et al., 2003; Mahley, 2016). Almost no cholesterol enters the brain from the peripheral circulation. However, small high density lipoprotein (HDL) particles may cross the BBB and transport cholesterol within the brain (Ladu et al., 2000; Koch et al., 2001).

Spherical lipoproteins similar to HDLs have been isolated from the CSF. They are composed of ApoE and ApoJ for the largest ones whereas smaller particles contain ApoAI and ApoAII. Astrocytes are the main producers of both ApoE (with microglial cells) and ApoJ (with neurons and ependymal cells) (Vance and Hayashi, 2010). Different isoforms of ApoE have been described in brain HDL particles (ApoE2, ApoE3, and ApoE4). ApoE is the main cholesterol carrier in the brain and is associated with Alzheimer's disease and other neurodegenerative disorders (Liu et al., 2013). Interestingly, cultured neurons and astrocytes expressing the ApoE4 isoforms display a reduced secretion of cholesterol and phospholipids, as well as a blunted lipid-binding capacity (Mahley, 2016). In addition, estrogens were shown to promote ApoE expression in microglia and astrocytes (Stone et al., 1997). Other brain apolipoproteins (i.e., ApoA-I, Apo-J, and Apo-D) may participate in cholesterol distribution via different receptors including LDL receptor, ABC (ATP-binding cassette receptor) -A1 and -A2 transporters, LDL Receptor-related protein, VLDL receptor, ApoE receptor 2, and megalin (Herz and Bock, 2002; Björkhem and Meaney, 2004).

In pathological conditions that lead to BBB loss of integrity, such as ischemic stroke, exogenous lipoproteins may enter the cerebral parenchyma and produce different effects. Functional HDL particles (HDLs displaying anti-inflammatory and antioxidant properties, see **Figure 5A**) are taken up by endothelial cells of the BBB in a thrombo-embolic stroke model of rat. Injection of fluorescent lipoproteins post-stroke are taken up by endothelial cells and astrocytes, but not by neurons (Lapergue et al., 2010). In this model and in the MCAO (middle-cerebral artery occlusion), one intravenous injection of HDLs isolated from healthy subjects reduced the mortality, the infarct volume and the hemorrhagic transformation associated with rtPA (recombinant tissue plasminogen activator) treatment (Lapergue et al., 2013). It is not known whether the cholesterol or steroids contained within these HDL particles are involved in the protective effects. It is indeed possible that either ester of steroids

or cholesterol delivery for local steroid synthesis could participate in neurogenesis and post-stroke remodeling. In this line, there is no study showing any beneficial effect of reconstituted HDL particles in CNS disorders. Noteworthy, these HDLs are composed of ApoA-I and phospholipids, but are devoid of cholesterol (Darabi et al., 2016). Ortiz-Munoz et al. recently demonstrated that at the acute phase of stroke, HDL particles are dysfunctional (HDLs displaying defective anti-inflammatory and antioxidant properties) and larger than in controls (Ortiz-Munoz et al., 2016). These qualitative abnormalities blunted their ability to protect the BBB during acute brain injury. In fact, in addition to their action on reverse transport of cholesterol, HDLs also display anti-oxidant, anti-inflammatory, and anti-protease activities (Tran-Dinh et al., 2013). These pleiotropic effects could be due to different proteins associated with HDL particles such as paraoxonase-1 (PON-1), but also to the lipids that they transport, and to steroids. In type 2 diabetes mellitus conditions (T2DM), HDL anti-inflammatory capacity is impaired due to decreased PON-1 activity (Ebtehaj et al., 2017). Another study investigated the association between plasma cholesterol/lipoproteins and BBB permeability in a condition of CNS inflammation such as multiple sclerosis (Fellows et al., 2015). HDL-Cholesterol was associated with lower levels of BBB injury and low CSF total protein concentration. The authors suggest that the BBB structural integrity is associated with plasma membrane subdomains involved in cholesterol homeostasis. HDL particles are larger in stroke patients than in controls and they display a reduced protective effect for the BBB (Ortiz-Munoz et al., 2016). Small HDL particles enter the CNS via SR-B1-mediated uptake and transcytosis (Balazs et al., 2004; Vitali et al., 2014). Morphological abnormality of HDLs in brain injury condition like stroke could be responsible for their reduced capacity to cross the blood-cerebrospinal fluid barrier. HDL supplementation could represent an interesting and innovative protective therapy for brain injury.

Interestingly, Leszczynski and Schafer (1991) demonstrated the interaction between lipoproteins and steroid hormones (androstenediol,  $17\beta$ -E2, DHEA, DHT, pregnenolone, and progesterone), highlighting a new pathway in steroid hormone processing in plasma and/or steroid hormone delivery to cells (Leszczynski and Schafer, 1991). Other reports also suggest that  $17\beta$ -E2 could be incorporated into HDL particles by lecithin:cholesterol acyltransferase under the form of  $17\beta$ -E2 ester, that could be in turn transferred into LDL particles by cholesteryl ester transfer protein LDL particles as reviewed in Tikkanen et al. (2002) and Höckerstedt et al. (2004). The **Figure 5B** illustrates such a transport of  $17\beta$ -E2 ester in HDLs and LDLs. These data would argue in favor of potential antioxidant, anti-inflammatory, and neuroprotective effects of HDLs implying cholesterol and other steroids (or their esterified forms) associated to lipoprotein particles. Indeed, estrogen derivatives with an unsubstituted A-ring phenolic hydroxyl group confers stronger antioxidant protection to LDL and HDL (Badeau et al., 2005). Such data could suggest a potential therapeutic use of HDL particles in order to improve their neuroprotective properties through their enrichment with steroids.



**FIGURE 5 |** HDL particles and sex steroids. **(A)** Lipoprotein particles display a central core containing cholesterol, cholesterol esters and triglycerides, that is enveloped by free cholesterol, phospholipids, and apolipoproteins. HDL particles display pleiotropic effects partly supported by their anti-inflammatory, anti-oxidant and neuroprotective properties. HDLs have been shown to display metabolic interaction with sex steroids (i.e., androstenediol, estradiol, DHEA, dihydrotestosterone, pregnenolone, and progesterone). **(B)** As suggested by Tikkanen et al. (2002),  $17\beta$ -E2 could be esterified with fatty acids by lecithin:cholesterol acyltransferase (LCAT) in HDL. Esterified  $17\beta$ -E2 could be subsequently transferred from HDLs to LDLs by cholesteryl ester transfer protein (CETP). Thus, HDL particles could be a source of cholesterol and steroids in the brain notably after CNS insults, and could be used as a carrier for improving steroids delivery in therapeutically approaches.

## CONCLUSION

In this review, we reported that the brains of fish, birds, and mammals are able to *de novo* synthesize a wide variety of sex steroids demonstrating that neurosteroidogenesis is an evolutionary conserved feature shared by common ancestors. We also emphasize that neurogenic regions are closely related to neurosteroid production. In particular, RGCs, acting as neural progenitors in the brain of adult fish, strongly express Aromatase B and some other steroidogenic enzymes, suggesting that RGCs are true steroidogenic cells. Such an expression of aromatase in RGCs is not restricted to fish as it was also observed in mammals during embryonic development (Martinez-Cerdeño et al., 2006) and in birds after mechanical lesion of the brain (Peterson et al., 2001).

Peripheral, we also highlighted the fact that the brains of fish, birds, and mammals are targeted by peripheral and locally-produced steroids namely estrogens, progestins, and androgens. It appears that nuclear and membrane-associated sex steroid receptors are widely expressed in the brains of vertebrates particularly in neuroendocrine regions (i.e., preoptic area and hypothalamus) as well as in neurogenic niches and neural progenitors, suggesting key roles of steroids in sexual behaviors and neurogenesis. Indeed, we notably depicted the roles of estrogens, progestins and androgens in constitutive and regenerative neurogenesis and in sexual behaviors. Due to their anti-inflammatory, antioxidant, and anti-apoptotic properties, sex steroids also exert neuroprotective properties in the brain, particularly after CNS insults such as stroke and traumatic brain



injury. However, the effects of steroids are not trivial to study and understand given that their actions are largely dependent on numerous variables (i.e., the timing, the concentration, the rhythm of exposure,...).

Peripheral steroids may diffuse or cross the BBB through transporters, raising the question of the respective roles of peripherally vs. centrally-produced steroids in brain homeostasis and functions. Peripheral sex steroid and neurosteroids can also act on the BBB permeability by modulating inflammatory and oxidative signals and consequently regulate brain homeostasis.

Of interest, in this review, we also discussed the potential hypothesis that the protective effects of HDL particles on stroke could be partly attributed to their interactions with sex-steroids. Thus, we raised the question of the contribution of cholesterol and sex-steroids transported by lipoproteins in the neuroprotection at the acute phase of stroke. Steroids are considered as good therapeutic candidates for CNS insults (i.e., stroke, traumatic brain injury), aging, and neurodegenerative

diseases. It opens a door for therapeutic research through the use of steroids alone, in cocktail, or transported to the injured site by HDLs.

## AUTHOR CONTRIBUTIONS

ND and EP designed the manuscript and supervised the work. ND, EP, TC, OM, CL, DC, VT, JN, and OK participated in the writing of the review. ND and CL made the figures.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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