Frontiers in Neuroendocrinology 30 (2009) 106–118

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

Neuroprotective actions of brain aromatase

Colin J. Saldanha [a,b,*], Kelli A. Duncan [a], Bradley J. Walters [a]

[a] Department of Biological Sciences, Lehigh University, 111 Research Drive, Bethlehem, PA 18015, United States
[b] Program in Cognitive Science, Lehigh University, Bethlehem, PA 18015, United States

ARTICLE INFO

Article history:
Available online 18 May 2009

Keywords:
Estrogen
Astroglia
Songbird
Testosterone
Neuroinflammation
Stroke

ABSTRACT

The steroidal regulation of vertebrate neuroanatomy and neurophysiology includes a seemingly unending list of brain areas, cellular structures and behaviors modulated by these hormones. Estrogens, in particular have emerged as potent neuromodulators, exerting a range of effects including neuroprotection and perhaps neural repair. In songbirds and mammals, the brain itself appears to be the site of injury-induced estrogen synthesis via the rapid transcription and translation of aromatase (*estrogen synthase*) in astroglia. This induction seems to occur regardless of the nature and location of primary brain damage. The induced expression of aromatase apparently elevates local estrogen levels enough to interfere with apoptotic pathways, thereby decreasing secondary degeneration and ultimately lessening the extent of damage. There is even evidence suggesting that aromatization may affect injury-induced cytogenesis. Thus, aromatization in the brain appears to confer neuroprotection by an array of mechanisms that involve the deceleration and acceleration of degeneration and repair, respectively. We are only beginning to understand the factors responsible for the injury-induced transcription of aromatase in astroglia. In contrast, much of the manner in which local and circulating estrogens may achieve their neuroprotective effects has been elucidated. However, gaps in our knowledge include issues about the cell-specific regulation of aromatase expression, steroidal influences of aromatization distinct from estrogen formation, and questions about the role of constitutive aromatase in neuroprotection. Here we describe the considerable consensus and some interesting differences in knowledge gained from studies conducted on diverse animal models, experimental paradigms and preparations towards understanding the neuroprotective actions of brain aromatase.

1. Introduction and general considerations

Steroids have long been studied for their acute, chronic and dramatic influences on the anatomy and physiology of the vertebrate brain [185,3,103,131,144]. The gamut of structural and functional endpoints affected by steroids has broadened far beyond the early paradigms of study which involved sexual behavior and aggression. It was these very studies, however, that identified 17β-estradiol (E_2) as an effector of many targets within the central nervous system (CNS). Perhaps more importantly, these studies were critical in broadening our understanding to include the brain as a source of steroids [221,222,224]. This conceptual shift was supported most strongly by learning that circulating androgens could be converted by neural tissue into E_2 [171]. The pluripotent effect of E_2 on behavior has attracted the attention of a diverse set of scientists in fields ranging from motor control to mood, onto learning and memory and further onto neuroinflammation, and brain damage [148,155,263].

Here we review a body of work implicating astrocytic aromatization as an important modulator of neurodegeneration and, possibly, repair [14]. Much is known about steroidal effects on degeneration and because this information is covered at length elsewhere in this issue, we begin with a broad overview of the neuroprotective effects of estrogenic precursors and discuss how aromatization may explain some of these effects. We focus our attention on the role of localized estrogen synthesis within the brain via the expression of aromatase and describe at some length the role of injury-induced aromatization in astroglia (see Fig. 1). We then consider some of the mechanisms whereby locally produced E_2 may mitigate degeneration. We conclude with some measured ideas on a comparative approach to further understanding the neuroprotective actions of aromatization within the CNS.

Neuroprotection may be defined simplistically as the prevention of neural degeneration [200,229]. This may be achieved by mechanisms that are (a) constitutively expressed and thus prevent or disallow harmful events, (b) rapidly activated (or inhibited) following brain damage to decrease secondary degeneration, and/

* Corresponding author. Address: Department of Biological Sciences, Lehigh University, 111 Research Drive, Bethlehem, PA 18015, United States. Fax: +610 758 4004.
E-mail address: colin@lehigh.edu (C.J. Saldanha).

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doi:10.1016/j.yfrne.2009.04.016

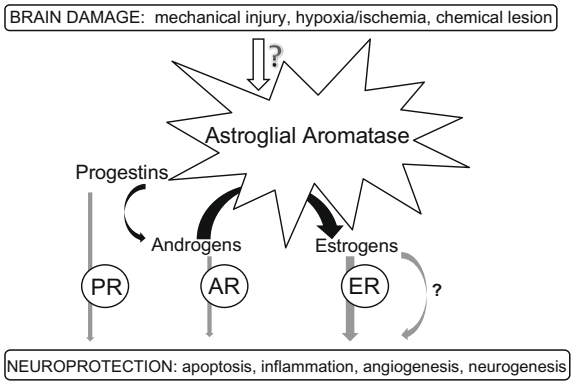

Fig. 1. This schematic represents the conceptual framework of this review. Brain damage results in an upregulation of aromatase transcription and translation in reactive astrocytes and radial glia (astroglia) in birds and mammals by mechanisms that are poorly understood. Components of the steroidogenic pathway including progestins and androgens themselves have some neuroprotective effects (gray arrows). However, it is often via their conversion to estrogens (black arrows) that these steroids may protect the brain from structural and functional degeneration. This influence is known to include, but is not limited to, actions on apoptotic and inflammatory pathways. Classical progesterone receptors (PR), androgen receptors (AR), and estrogen receptors (ER) have all been implicated in these effects, although some data do support estrogenic effects on neuroprotective mechanisms via ER-independent pathways.

or (c) regenerative events with rapid turnover resulting in the replenishment or repair of damaged circuits. Several lines of evidence demonstrate that estrogens and their precursors are neuroprotective in the CNS via a diverse set of mechanisms including the modulation of apoptotic cell death [26,38,60,233,234], antioxidant activity [19,24,107,189], neuronal and glial cell proliferation [57,36,94,102], and elevations in neurotrophic factors [35,98,97].

Our understanding about the estrogenic modulation of brain and behavior is well grounded in our ideas about the sites and regulation of estrogen synthesis in many vertebrates. Across phyla, cytochrome P_{450} aromatase is the product of the *cyp19a* gene, or gene duplicates, and is best known for its role in the conversion of C19 androgens into C18 estrogens [236]. Consistent with this function, aromatase is expressed in the ovaries [246], adrenal glands [168] and testes [50]. However, aromatase expression is not limited to classical endocrine glands, but is present in many different tissues and cell types where it may be expressed constitutively or transiently depending on stage of development, pregnancy, injury, or disease [237]. Examples of other tissues with readily measurable levels of aromatase expression include bone [273], adipose [63], fetal liver [253], placenta [161], skin [282], breast cancer [39] and brain [173,172]. It is noteworthy that aromatase expression in the gonads and the brain appears to be conserved across the widest range of species representing most, if not all, vertebrate taxa [236,41]. While gonadal aromatization is well studied for its role in reproduction, over the past decade, neural aromatization has garnered interest for its role in many aspects of neuroplasticity including neuroprotection.

1.1. The role of estrogenic precursors in neuroprotection

Aromatase is often regarded as the final enzyme in steroidogenesis, although further modification of its estrogenic product is certainly well established [150,281]. It is perhaps not surprising that many estrogenic precursors can be neuroprotective, often via their ultimate conversion to estrogens. Notably, many estrogenic precursors are themselves directly neuroprotective, but some clearly interact with aromatase or estrogen and thereby exert their neuroprotective effects.

Despite fluctuations in local and circulating cholesterol following ischemic [127] and traumatic injuries [179], there are relatively few studies that directly examine the effects of cholesterol on neuronal survival, turnover, or branching. Some studies suggest that cholesterol may play a neurodegenerative role in amyloid β (Aβ) toxicity [190,22], though other studies suggest neuroprotective roles [243]. Interestingly, decreased cellular levels of cholesterol [1] or inhibition of cholesterol synthesis, *in vivo* or *in vitro*, enhance cell survival [21,20,114,27,151]. Similarly, the cholesterol synthesis inhibitor simvastatin also appears to increase neurogenesis [267]. In addition, the steroidogenic acute regulatory protein (StAR), which transports cholesterol to the inner mitochondrial membrane where it can be used for steroidogenesis, is increased upon brain injury [232]. Finally, a recent study has examined the role of glial derived cholesterol in neurite branching and synapse formation, demonstrating that this cholesterol is ultimately aromatized to estradiol, which results in increased synaptogenesis [79]. Therefore, it appears that if cholesterol exerts neuroprotective actions, they may occur because of its catabolism. However, this conclusion must be tempered, and will require much more investigation. Indeed, some studies suggest that there are non-steroidal cholesterol metabolites that are neuroprotective [275], though this may again be indicative of the resultant decreases in cholesterol upon metabolism [23].

Cleavage of the cholesterol side chain by the *cyp11a* gene product results in the steroid hormone pregnenolone (P5), which in turn can be converted to progesterone (P4) by the enzyme 3-beta-hydroxysteroid dehydrogenase (3β-HSD) [6,165]. Both P5 and P4 have been shown to increase neuronal survival and proliferation. Specifically, progestins promote neuronal survival under various types of stress, including traumatic brain injury [202,258,207], ischemia [40,101,126], excitotoxicity [129] and chemotoxicity [259,44]. P5, the first true steroid in the steroidogenic pathway, increases neurogenesis and reduces neuronal death in brain cell cultures [152]. In mouse hippocampal cells P5 protects against glutamate and amyloid beta protein toxicity [109] and prevents hippocampal neuronal death induced by kainic acid *in vivo* [259]. P4 is synthesized from P5 via the enzyme 3β-HSD and also exhibits neuroprotective properties. Administration of P4 reduces the number of fibers with myelin abnormalities in the sciatic nerve of STZ-treated rats [260] and is neuroprotective in nerve crush injury [204]. P4 also promotes behavioral recovery and decreases cell death [157,158].

Other studies have demonstrated that these steroids are neuroprotective at least partially, via their ultimate conversion by aromatase to estrogens or via their interactions with aromatase and/or estrogens [203,259]. Estrous females are more protected against brain injury than proestrous females, suggesting that ovarian hormones including P4 play a role in neuroprotection [264,206]. Some of these studies suggest that P4 can exert neuroprotective effects via P4 receptors (PR), while others demonstrate a receptor independent mechanism, or even more specifically, a dependence upon aromatization [70,225,226]. However, exposure to P4 can also diminish estrogen mediated neuroprotection by downregulating neuronal estrogen receptor (ER) expression [4,51,125,208].

Successive hydroxylation and lyation of progestins results in androgen synthesis. Both of these reactions are catalyzed by the enzyme *cyp17* alpha hydroxylase [165]. While there is some evidence for a degenerative role of androgens in development and sexual differentiation [9], there appear to be many more reports confirming the neuroprotective properties of androgens *in vitro* and in adult model systems. Several *in vitro* studies demonstrate that dehydroepiandrosterone (DHEA) enhances neuronal and glial survival [201,32], while testosterone (T) increases neuronal survival, the number and receptive field of neurite processes, and neurotransmitter output [130,248]. Also, T has been shown to increase

neurite length [199], angiogenesis [133], and neurogenesis [133,7,143]. Several other *in vitro* studies suggest that T and DHEA mitigate neural cell death that is induced by several different stressors including, excitotoxicity [48], chemotoxicity [132], serum deprivation [56,110], oxidative stress [5,59] and amyloid beta misexpression [278]. *In vivo*, castration of adult male rats results in decreased hippocampal cell survival, and replacement with T or DHT increases neurogenesis [244]. T has also been shown to increase neuronal turnover in the songbird HVC [195,194] (and in the amygdala of adult male meadow voles [86]. Further *in vivo* studies have corroborated the neuroprotective effects of T and DHEA against ischemically and chemically induced degeneration [259,140,141]. T increases neuronal survival, regeneration, and pivotal regulation of peptides associated with higher risks of Alzheimer's disease [12,29]. Following injury, T regulates expression of glial fibrillary acidic protein (GFAP), an astrocyte specific intermediate filament protein that increases with age in reactive astroglia [29]. T also reduces apoptosis in primary neuronal cultures of human cells [110]. Whereas, T administered after injury reduces reactive astrogliosis [18]. In the developing rat cervical ganglion, androgens increase volume and both the number of neurons and synapses [265]. DHEA protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mouse striatal DA neurons [264,68] and kainic acid-induced death in rat hippocampal hilar neurons [259,264].

Although dihydrotestosterone (DHT), a non-aromatizable androgen has also been reported as neuroprotective [203,139,146,147] DHT administration after injury has no effect on reactive astrogliosis, suggesting that the role of T in regulating reactive astrogliosis is due to the conversion to estradiol by aromatase [18]. Since both T and DHEA can be ultimately converted to estrogen by aromatization, it is possible that these steroids may be neuroprotective directly or by their conversion to estrogens if aromatase is being expressed at appreciable levels.

2. Brain aromatization and neuroprotection

There is good reason to consider the neuroprotection afforded by many estrogenic precursors as due to their ultimate aromatization to neuroactive estrogens. The aromatization of androgenic substrates within the brain itself continues to provoke tantalizing questions about the neuroendocrine nature of the vertebrate brain. Recently, a considerable body of evidence strongly supports a neuroprotective role for encephalic estrogen synthesis particularly following brain damage resulting from anoxia/ischemia, excitotoxicity or mechanical injury.

Garcia-Segura et al. [95] first suggested an important distinction between constitutive and induced aromatase expression in the vertebrate central nervous system. While the expression of aromatase in brain had been previously described [144], this constitutive expression was shown to be exclusively neuronal and limited to hypothalamic and some very circumscribed limbic areas in mammalian brain including the amygdala and bed nucleus of the stria terminalis (BnST) [174]. Neuronal perikarya expressing aromatase immunoproduct were described in species as diverse as Japanese quail (*Coturnix japonica*), rat (*Rattus norvegicus*), African green owl monkeys (*Cercopithecus aethiops*) and humans (*Homo sapiens*) [174]. Upon the induction of brain damage via excitotoxicity or mechanical injury, however, aromatase expression was not only induced in many brain areas including the hippocampus, striatum, cortex and corpus callosum, but was localized to reactive astrocytes [95,52]. These studies clearly identified glial cells as capable of aromatase expression and suggested an association among brain damage, repair, and astrocytic aromatization. It should be noted that antibodies which specifically and reliably target mammalian aromatase have been surprisingly and notoriously whimsical. However, almost all the data mentioned above have been well supported by studies using aromatase activity as an endpoint, underscoring their validity and the unequivocal increase of aromatase following brain damage. This increase is best explained as occurring within reactive astrocytes.

Interestingly, astroglial aromatization had been described previously in primary cultures of developing songbird brain [223]. In these experiments, primary dissociated cultures from hatchling zebra finches (1–6 days old) were examined for aromatase activity at 7,14, 21, or 28 days *in vitro*. Surprisingly, while protein content of these cultures reached asymptote in about 7 days, and neuronal death was almost complete in about 21 days, aromatase activity increased with age of culture. Indeed, *in situ* hybridizations using antisense aromatase probes revealed that astroglia did contain the aromatase transcript providing additional and independent verification of the presence of aromatase in these cells. These data suggested the possibility that the bed of confluent astroglia was a considerable source of aromatization that was upregulated as the age of the cultures increased. Although the physiological significance of these findings was unclear, astroglial aromatase expression was confirmed and extended by Zwain et al. [284] where both aromatase mRNA and estradiol (E_2) were detected in purified astrocytic cultures of mammalian brain. Perhaps most notably, these *in vitro* studies were pivotal in identifying factors that likely regulate aromatase in astrocytes, but not neurons or oligodendrocytes. Together, these studies set the stage for further work on aromatase expression by a novel cell type, the astrocyte. However, the physiological significance of astrocytic aromatase expression remained enigmatic.

Azcoitia et al. [13] presented primary and convincing evidence for neuroprotection by brain aromatase in vertebrates. In a series of experiments that manipulated, (a) peripheral hormone titers, (b) peripheral and central inhibition of aromatase and (c) genetic complement, these researchers were able to establish a critical role for this enzyme in the protection of vertebrate neural circuits from excitotoxic injury. Briefly, using mice as the animal model, the observation that the susceptibility of hippocampal neurons to excitotoxicity, was reduced in the presence of circulating aromatizable androgen and estrogen, but not non-aromatizable androgens strongly suggested that the conversion of C19 androgens to C18 estrogens was an important step in rodent neuroprotection [13]. Next, the exacerbation of excitotoxicity by peripheral and central inhibition of aromatase implicated cerebral aromatization as key in this neuroprotection. Finally, the observation that mice null for the aromatase gene (ARKO) were especially vulnerable to excitotoxic brain damage relative to their wild-type counterparts, underscored the importance of aromatase in neuroprotection.

These findings were well supported by studies on aromatization and mechanical brain damage in the songbird. In this animal model, central administration of the aromatase inhibitor, fadrozole, dramatically increased the volume of damage in the adult male zebra finch brain [268] and replacement with E_2 prevented the exacerbation of damage by aromatase inhibition [215].

3. Astroglial aromatization, degeneration and cytogenesis

3.1. Effects on secondary degeneration

There is general agreement that the manner in which upregulated aromatase affects neurodegeneration is via the inhibition of secondary, apoptotic damage. More specifically, TUNEL labeling in the songbird suggested that treatment with the aromatase inhibitor fadrozole increased, and concomitant E_2 administration decreased, the number of cells undergoing apoptosis 72 h post

primary insult [268,215]. Interestingly, there was no difference in the degenerating cells labeled by Fluoro-Jade-B, a marker that does not distinguish between pyknotic and apoptotic cell death and TUNEL. This finding suggested that the effect of aromatization on injury-induced secondary degeneration may occur by a specific, and perhaps exclusive modulation of apoptotic pathways. In fact, aromatase-dependent inhibition of apoptosis is well established in peripheral organs and in breast cancers [33,54,55,83,142]. Further, this idea is in excellent agreement with the observed increase in apoptosis in aromatase knockout mice [115] and with more sophisticated measures of apoptosis used in the mammal where E_2 replacement is known to affect Bcl-2 expression [196].

Although it is very difficult to directly compare experiments across species, nature of neural insult, and measures of degeneration, the neuroprotective role of induced aromatase may be more dramatic in songbirds relative to mammals. Notably, the wave of secondary degeneration characteristic of mammalian brain damage is only detectable in the songbird brain following inhibition of injury-induced aromatase. These data suggest that songbirds may have evolved a rapid and robust endogenous mechanism of neuroprotection [269]. These findings are corroborated by the effects of androgens and estrogens, the local levels of which are likely altered by aromatization, [216] on various indices of apoptosis and are more completely described elsewhere in this issue.

3.2. Effects on cytogenesis and migration

Damage to the vertebrate brain also induces aromatase expression in radial glia as well [184]. Although we cannot rule out a role for aromatization within radial glia on secondary degeneration, this cell type is perhaps more involved with the regulation of cytogenesis and cell migration following neural damage. Although these processes may not be considered neuroprotective in the strict sense, they may critically modulate regenerative and restorative aspects following neural damage. Radial glia have long been studied as important scaffolds of neuronal migration during development [112,113]. More recently, the presence of radial glia in the adult CNS [247] and their potential role in restorative processes following neural injury [210,274,205] have been intensely studied. The studies of Peterson et al. [184] convincingly demonstrate that injury-induced mitotic cells aggregate around, possibly contact, and appear to migrate along injury-induced aromatase expressing radial glia. Thus, aromatase expression in radial glia may be key in the processes of neuronal migration towards the restoration of brain structure and function following brain damage. Indeed, systemic treatment with fadrozole does reduce the number of injury-induced mitotic cells in the subventricular zone of the songbird brain [137] suggesting that astrocytic aromatization may also contribute to cell proliferation. However, it is currently unclear whether or how peripheral aromatization may contribute to this effect. More importantly the cell type(s) of injury-induced mitotic cells remains unknown. It is exciting, however, to consider the possibility that brain aromatase may modulate repair mechanisms such as cytogenesis, neural fate, neural migration and survival as contributors to the set of mechanisms that promote the protection of neural circuits.

4. What initiates aromatase expression in astroglia?

4.1. Molecular mechanisms of glial aromatase expression

Since the neuroprotective effects of brain aromatase after injury appear dependent upon its expression in reactive glia surrounding the damaged area [13], discovering the mechanism by which aromatase is upregulated after injury is of critical importance. Currently, most of our information about the regulation of aromatase transcription comes from data in human cells or in non-human primates [237]. In humans and other mammals, aromatase transcription in the ovary is initiated by steroidogenic factor-1 and CREB binding to promoter II (1d) [246]. In adipose tissue, expression is induced by class I cytokines combined with glucocorticoid signaling acting on promoter I.4 (1b) [235,279]. Aromatase expression in the brain may be more convoluted still; neural expression first thought to be driven by isoform 1F is now known to be modulated by multiple promoters perhaps in multiple brain areas, and across multiple species [272,271]. These transcripts include several expressed predominantly or exclusively in brain and others also expressed in peripheral tissues [271,116,219]. Whether or not the induction of these brain transcripts represents regulation similar to that seen in adipose, ovarian, or other tissues, is as yet unresolved.

To narrow the possibilities, Yague et al. [272] tested several different aromatase inducing factors on human glioma cells *in vitro*. The treatment of T98G cells with several different factors suggested that glial aromatase expression can be regulated by multiple promoters, namely those associated with exons I.3, I.4, I.6, I.7 and PII. Interestingly, exposure to the synthetic steroids dexamethasone or mifepristone, or to vitamin D, resulted in the upregulation of several of these transcripts in the glioma cells, but not in breast cancer or neuroblastoma cell lines. In the songbird brain, another model for aromatase upregulation in reactive astrocytes after injury, there are only two known promoters in the *cyp19* gene, a brain form and an ovarian form [193]. Direct shotgun sequencing of neuronal and injury-induced transcripts of aromatase in the zebra finch brain revealed no differences in any of the exon sequences, suggesting that, if zebra finch *cyp19* has multiple promoters, they likely do not result in changes in mRNA splicing or sequence [270].

Accordingly, a silencing element has been identified in the sequence upstream of exon II, and transcription in breast cancer cells and skin fibroblasts can be suppressed by a number of different proteins [280]. And in ovarian granulosa cells, the nuclear receptor proteins NURR1 and NGFI-B similarly downregulated aromatase transcription [266]. Whether or not these silencing factors play a role in the differential expression of aromatase in the homeotherm brain remains to be elucidated. Taken together, however, this set of alternate promoters and silencing elements provide a range of possibilities in terms of candidate mechanisms to control the regulation of aromatase transcription in glia.

Interestingly, in some species, reactive astrocytes are not the only glial cells that express aromatase. In the zebra finch brain, radial glia proximal to injury are also reactive and upregulate aromatase [184]. Given that radial glia in the songbird brain do not express aromatase post-hatching or after injuries more distal to the ventricular zone, it is likely that aromatase expression in these cells is being upregulated by a similar mechanism to that operating in reactive astrocytes. Several species of teleost fish appear to express aromatase in the radial glia of the forebrain, but in this case constitutively and throughout life [84,136,162,182]. In zebrafish, this aromatase is the product of a separate aromatase gene, *cyp19b*, appears to be expressed solely in radial glia, and is upregulated in a cell specific manner by exposure to estrogen via a non-canonical estrogen response element in its promoter sequence [136,163]. Combined, these studies tell us that glial aromatase expression is likely regulated in a manner that differs from constitutive neuronal aromatase, and that this regulation most likely differs across species. Such different modes of expression suggest that these animals may provide powerful models for studying the mechanisms of glial aromatase expression *in vivo*.

The question of how aromatase transcription is being differentially modulated in glia versus neurons, or in the injured versus

uninjured brain, is a question of tremendous importance that has yet to be resolved. It will be invaluable to experimental and therapeutic science to determine whether or not transcription in glia is induced or disinhibited by injury, and the mechanism by which this occurs. Such information would allow for experimental manipulations of glial aromatase in the absence of injury, and could present a means for localizing an estrogenic neuroprotectant without affecting circulating levels of steroids. Additionally, further characterizing the regulation of glial aromatase could dramatically enhance our understanding of the effects of gonadal and neural steroids on sex differences, sex behavior, and numerous other demonstrated and proposed actions of brain aromatization.

4.2. Diffusible factors as regulators of astroglial aromatization

To the best of our knowledge, aromatase induction in astroglia seems to occur following damage to the vertebrate brain regardless of the nature of this perturbation. This damage can involve multiple physiological mechanisms including pyknosis of mechanically damaged cells in the area of injury and/or the induction of inflammatory cascades resulting from the compromise of the blood brain barrier. It is reasonable to consider the hypothesis that factors released during such events may prove key in regulating aromatase transcription and translation around the site of primary damage.

Primary damage to the vertebrate CNS begins with the dying of cells immediately adjacent to the site of injury. This necrotic death results in an abundance of extracellular cations and glutamate [11,178]. These changes are known to activate astroglia around the site of injury and may be important transcription factors for genes within astrocytes and radial glia [181]. Microglia, which are activated in response to compromise of the blood brain barrier are secretors of cytokines. These cytokines are also potent modulators of astrogliosis. Indeed, reactive astrocytes contain receptors for glutamate, interleukin 1 (IL-1), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and express cationic channels on their membranes [53]. It follows that cations, glutamate, and cytokines may influence the expression of aromatase in astroglia, and thus are excellent candidates for the rapid upregulation of aromatase around the site of injury. However, despite being strong candidates there is a relative paucity of information with regards to a specific role for many of these factors in the regulation of aromatase expression. Surprisingly, treatment of pure astrocytic cultures with the cytokine (IL-1) resulted in a dose-dependent inhibition of aromatase transcription and E_2 formation *in vitro* [284]. Further, treatment with glutamate agonists decreases aromatase activity in quail hypothalamic explants [17]. However, addition of dibutyril cAMP dramatically increased aromatase activity and mRNA, but only in cultures of songbird brain that were mostly astroglial, with few or no detectable surviving neurons [87]. Thus, despite some evidence implicating calcium dependent processing, there remains plenty to learn about the regulation of aromatase expression around sites of damage in the vertebrate brain.

5. How is induced astroglial aromatase neuroprotective?

While the mechanisms of aromatase neuroprotection are most likely mediated by local estrogen synthesis, it is important to note that several different isoforms of estrogens can result from aromatization (estradiol, estrone, 2-OH-estradiol, and the 17alpha and beta stereoisomers) many of which have demonstrated neuroprotective properties [25,67,153,250]. Additionally, brain aromatization may also affect the local concentrations of C19 and C21 steroids (androgens and progestins) which may be depleted. However, the roles of estrogens in promoting neuronal survival, mitigating degeneration, and even promoting recovery have been characterized to a great extent and in some detail. Estrogens are protective under numerous types of stressors, including oxidative stress [25,100,220], glutamate excitotoxicity [239,245], chemical lesions [198], traumatic or mechanical injuries [153], ischemia [196,257], iron toxicity [67,197], glucose or serum deprivation [62,106], and specialized disease related pathogens such as Aβ [105,82], and HIV proteins [66,213].

The breadth of the available data on estrogen mediated neuroprotection stands in stark contrast to the relatively few reports that have directly investigated neuroprotective roles for brain aromatase. Those that do exist come primarily from the aromatase knock-out (ARKO) mouse model, pharmacological inhibition of aromatase, or from correlational studies in humans. Genotyping of human individuals suggests that the brains of female Alzheimer's patients have reduced levels of aromatase [123,277], and that certain aromatase gene polymorphisms are associated with increased or decreased incidences of the disease [64,65,119,121]. In mouse model studies, ARKO animals have serotonergic and dopaminergic impairments, and greater degeneration in response to domoic acid or MPTP-induced toxicity when compared to intact and gonadectomized wild type animals [13,167]. In addition, ARKO and fadrozole treated mice demonstrate greater cortical and striatal damage than intact and ovariectomized control animals after ischemia induced by occlusion of the middle cerebral artery (MCAO) [154]. Inhibition of aromatase with fadrozole in intact male rats had no effect on hippocampal degeneration, but when coupled to kainic acid administration, fadrozole greatly exacerbated degeneration as compared to animals treated with kainic acid alone [13]. Similarly, in intact male zebra finches, secondary degeneration of neural tissue surrounding a primary mechanical injury is almost undetectable, however, upon local inhibition of aromatase with fadrozole, cell death as measured by both TUNEL and Fluoro-Jade-B labeling is dramatically increased [268,215,269]. These studies suggest a direct neuroprotective role for aromatization under the stressors of injury and degenerative disease.

Recent data strongly suggest that injury-induced aromatase elevates local estrogens. This increase results in activation of microtubule associated protein kinase (MAPK) signaling pathways which act synergistically to activate (phosphoinositol-3 kinase) PI3K/Akt (protein kinase B) signaling [69,149]. PI3K/Akt signaling has been shown to be instrumental in the activation and expression of antiapoptotic factors, including members of the bcl-2 family [69]. Consistent with this proposed mechanism, IGF-I has been shown to be neuroprotective against neurodegenerative stimuli, enhance synaptic plasticity, and improve functional outcomes after brain injury [47]. These neuroprotective effects have been shown to involve Akt signaling, and antagonism of IGF-I receptor (IGF-IR) has been shown to prevent the estrogen induced upregulation of bcl-2 [192,191]. Also, estradiol has been shown to activate PI3K/Akt [69,192], modulate bcl-2 activity [69,240], and increase the expression of IGF-I, IGF-IR, and IGF binding proteins [47,46]. While a direct link between aromatase and Akt signaling remains to be established, this interaction presents a promising explanation of the neuroprotective effects of brain aromatase.

5.1. Steroidal consequences of aromatization

We previously discussed that many of the neuroprotective actions in the brain could be accounted for by aromatase acting to increase local estrogen levels. During steroidogenesis, aromatase synthesizes estrogens via two different pathways. One pathway converts androstenedione to estrone, while a second pathway converts T to estradiol [171]. As of result of this conversion, estradiol and estrone levels are increased while T and androstenedione levels may be decreased. It is important to note, that while aromatase

can increase both estrone and estradiol levels, circulating levels of androstenedione are much lower than T, thus the neuroprotective effects of aromatase after injury are most likely, and correspondingly widely accepted to be the result of increased estradiol. Brain-derived estrogens after injury have been studied extensively and are examined previously within this review. Upon MCAO in male rats, plasma estradiol concentration remains constant, while estradiol levels in the parabrachial nucleus and the central nucleus of the amygdala are increased [216,217]. The increase in amygdalar estradiol was ablated by local injection of the aromatase inhibitor letrozole into the central nucleus [216]. Several studies also demonstrate that degeneration caused by aromatase inhibition can be mitigated by concomitant administration of estradiol. Specifically, in a rat model for cerebellar ataxia, and a zebra finch model for traumatic brain injury, fadrozole increased, and estradiol decreased, neurodegeneration [232,215], suggesting that local aromatase does synthesize estrogens in response to insult and that neuroprotection is achieved via this estrogen synthesis. A quick synopsis of the research would suggest that estrogens are neurotrophic, neuroprotective, and promote synaptic plasticity and neuronal survival across vertebrates (see [96] for review). However, high levels of estrogens can be dangerous and have been shown to be neurotoxic in neurons located in the hypothalamus [96,71,117]. Thus another mechanism underlying the role of aromatase on neuroprotection could be that its increased expression after injury leads to a distinctive steroidal profile. These steroidal consequences of aromatization may include; (1) decreased levels of androgens, (2) upregulation of estrogen from T (and/or the T precursors P5, P4, and DHEA) and (3) aromatase driven metabolism of estrogens into catecholestrogens that in turn promote neuroprotection.

Several studies have demonstrated correlations between neuroprotective action and low levels of androgens. In male zebra finches, castration results in increased neuron number in adult birds [10]. Correspondingly, low levels of circulating androgens were able to promote neurogenesis and neuronal survival. These findings are supported by mammalian data that show that females are more protected from brain injury than males, possibly due to decreased circulating androgens [96,209,120] These data suggest a possible neuroprotective role for low levels of circulating androgens, however the majority of past research suggest that low levels of androgens are detrimental and not neuroprotective in the brain. Levels of bioavailable T decline in the brain as a consequence of aging, thus these animals provide an interesting model for identifying the role of decreased androgens on neuroprotection [175]. As gonadal steroid levels decline in aged animals, an associated increase in neurodegeneration has been observed [15]. Lower T levels are also associated with increased GFAP expression [176], reactive astrocyte hypertrophy and neurodegeneration in rats [29]. These data suggest that while low levels of androgens can serve a neuroprotective role, low levels of androgens are most likely neurodegenerative rather than neuroprotective. Thus, low levels of androgens as a result of aromatization do not appear to regulate neuroprotection. Another steroidal outcome of aromatization is the possible upregulation of estrogen precursors such as P5, P4, Androstenedione, Androstenediol, and DHEA.

Following traumatic brain injury, local levels of P5 and P4 are increased in both the brain and spinal cord [15,74]. P4 biosynthesis is also upregulated in the spinal cords of rats with streptozotocin (STZ) induced diabetes [218]. Thus it is likely that estrogen precursors could play a role in aromatase-mediated neuroprotection since they may be upregulated under similar conditions as aromatase. The mechanisms underlying the role between increased estradiol and P4 and P5 synthesis have yet to be identified, however in rats, estradiol stimulates upregulation of 3β-HSD mRNA expression and activity thus increasing the levels of P4 in the hypothalamus and enriched astrocyte cultures [242,238,164]. When aromatase activity is blocked, the neuroprotective effects of P5 and DHEA are eliminated, suggesting that estradiol formation by aromatase mediates neuroprotection by these steroids [259,159,160]. Therefore another potential mechanism underlying aromatase and neuroprotection could be the subsequent increase in locally produced P5, which is ultimately aromatized [259].

The catecholestrogen, 2-OH-estradiol, is produced from estradiol by 2-hydroxylase. Increased expression of 2-hydroxylase has been correlated with increased aromatase activity and is even one of the multiple functions of aromatase [16,180]. Like estradiol, 2-OH-estradiol binds to the ER and has a number of neuroprotective effects. Hippocampal HT22 cells challenged with hydrogen peroxide were protected against injury when treated with 2-OH-estradiol [250] and 2-OH-estradiol protects against iron-induced neuronal cell death in primary cultures of chick embryonic neurons and ischemic brain damage in male mice [67]. Catecholestrogens can be further metabolized by COMT and are able to modulate the synthesis, metabolism, and binding of catecholamines that have previously been shown to modulate ischemic brain damage [145,134]. However, it is important to note that under certain stressors, catecholestrogens may not provide neuroprotection, and that some catecholestrogens may even enhance degeneration. For example, in ovariectomized rats, kainic acid induced hippocampal degeneration was not mitigated by 2-OH-estradiol nor by 2-methoxy-estradiol, and the latter was even degenerative in the absence of kainic acid [186].

5.2. Steroid receptors and injury

Under the classic model of steroid receptor action, steroids produce their characteristic responses by binding to their steroid receptor, which then initiates gene specific transcription and translation. Thus identifying the role of steroid receptors in neuroprotection is key to fully understanding the potential role of aromatase. Steroid receptors are expressed in both neurons and in non-neuronal cells in vertebrates, more specifically ER, AR, and PR are all expressed in glial cells under normal and neurodegenerative conditions [93]. Neural injury upregulates ER in astroglia and AR in microglia [92]. In the cerebral cortex, injury-specific upregulation of ER-α and downregulation of ER-β expression has been reported [92,76] Interestingly, injury induced upregulation of ER is significantly higher in regions of the cerebral cortex that produce higher levels of ER developmentally [230,276]. Garcia-Segura et al. [95] propose that neuroprotection and subsequent neuronal repair involves the re-initiation of developmental programs involving higher expression of ERs by injured neurons [96].

5.3. Aromatization, ER and neuroprotection

Classically, estradiol mediated neuroprotection is due to the transcriptional activity of estrogens activating two nuclear receptors, ER-α and ER-β [177,169]. Following aromatization, estrogen levels are likely increased at the site of injury and estrogens have been shown to alter ER-α expression in a tissue specific manner. In rat hippocampal slices, estrogen treatment increases expression of ER-α [212]. This increase in ER expression is also seen in adipose, uterine, and liver tissues [75,166,122]. Thus, a possible mechanism underlying aromatase-mediated neuroprotection is the local increase in estradiol that subsequently increases ER-α expression and thus produces genes and proteins that promote neuroprotection. An alternative hypothesis could be that other steroids (T or P4) could alter ER expression and thus promote or attenuate neuroprotection. Studies of birds with low levels of circulating androgens show that ER-α expression is increased as a result of low levels of androgens [89,45,90]. These data support the role of

aromatase in mediating neuroprotection. However, P4 which is upregulated by estradiol and injury decreases ER expression [124]. Thus P4 has the ability to attenuate the neuroprotective actions of estradiol via ER downregulation.

The role of ERs in mediating neuroprotection is well documented. Following lesioning, ER-α but not the AR is expressed in reactive astrocytes [92]. When estradiol is given and ER-α binding is eliminated estradiol fails to protect against cell death [78]. Corroborating this neuroprotective role of ER-α, ER-α expression is decreased in hippocampal neurons of Alzheimer disease patients [118]. Using ER-α and ER-β knock out animals Dubal et al. [77] showed that ER-α and not ER-β is pivotal to estrogen-dependent neuroprotection as a result of ischemic brain injury.

Despite ER-α being the primary receptor mediating neuroprotection, a role for ER-β has been postulated. ER-β knockout mice undergo increased neuronal loss [262] and Dubal et al. [78], reported that ER-β may play a role in cessation of cellular death after middle cerebral artery occlusion (MCAO) by increasing neurogenesis and regeneration. However, ER-β expression is lower in estradiol treated animals and in the absence of ER-β, estradiol is still neuroprotective [78].

Toran-Allerand [255] recently identified a novel plasma membrane associated ER (ER-X) in brain and uterus [255]. ER-X is developmentally regulated and is re-expressed after ischemic brain injury in mice with Alzheimer's disease. ER-X is distinct because it is inhibitory and does not elicit ERK activation like ER-α and ER-β [254,256]. However, it is also possible that these membrane associated receptors may actually represent isoforms of ER-α or ER-β that are transiently expressed at the membrane. Additionally, GPR-30, a novel membrane bound G-protein receptor that is expressed in the brain [34,88], has a high affinity for estradiol, and an ability to activate ERK signaling [49,81,80]. Therefore, GPR-30 may present a plausible mechanism for the neuroprotective effects of estrogens. Regardless, several studies support a role for membrane bound ERs in neuroprotection since estradiol conjugated to various membrane impermeable proteins has been shown to promote neuroprotective actions [73,108]. Importantly, these neuroprotective effects are ablated by ER antagonists [73,108].

5.4. Aromatization, AR and neuroprotection

Steroid levels can mediate the expression of AR. Therefore, if local aromatization is downregulating local androgen levels, it may also be downregulating AR expression. This idea is contraverted by the demonstration that ARs are upregulated in astrocytes and microglia after injury [92], however, it may take prolonged exposure for ARs to be downregulated, or they may be differentially regulated in neurons, or also inversely regulated by some other product of injury.

Although ERs primarily mediate neuroprotection, ARs also play a considerable role. AR dependent neuroprotection is delayed in human primary neurons and protects neurons against serum deprivation [110]. Unlike reactive astrocytes that express ER-α after lesioning, microglia express AR and not ER-α after injury [92]. These findings suggest a potential role for androgens in neuroprotection.

5.5. Aromatization, progestins and other modulators of neuroprotection

P4 is neuroprotective and estradiol increases PR expression. PRs are unique in that there are both ER-insensitive and ER-sensitive PRs and estrogens upregulate PR expression across mammals [70,138,30,28,231,252,227]. Following injury, PR expression is increased in the spinal cord [70]. These data suggest an alternative mechanism for neuroprotection for estrogen induced increases in both P4 and PR levels, and similarly, it is possible that modulated PR expression could be playing a role in aromatase action.

Activation of ER, is pivotal to the neuroprotective effects of aromatase following injury and identifying how all aspects of steroid receptor action relate to neuroprotection is key. Tamoxifen and Raloxifene, both selective ER modulators (SERMs), are neuroprotective. Both SERMs enhance synaptic density and stimulating neurite outgrowth [72]. Additionally, Tamoxifen protects against permanent MCAO neurodegeneration in rats [261]. Furthermore in microglia, both tamoxifen and raloxifene decrease brain inflammation by activating ERs [249]. These studies suggest a potential therapeutic role for SERMs following brain injury.

In addition to the steroid receptors and their selective modulators, receptor coactivators may be considered candidates that aid in neuroprotective processes. Steroid receptor coregulators act by enhancing or depressing the activity of the steroid receptor to which they are associated [156,228]. Previous research has shown that coregulators can play a role in steroid sensitive behaviors and their involvement with steroid sensitive cancers has also been studied [251,58,91]. To date, there is no data identifying the potential role of these proteins in altering neuroprotection. Identifying whether or not steroid receptor coregulators play a role in aromatase based neuroprotection would not only enhance our understanding of this phenomenon, but would also inform many other aspects of steroid mediated neuroprotection as well as provide a potential means for manipulating and possibly enhancing aromatase induced neuroprotection to achieve both experimental and translational aims.

6. Is constitutive aromatase neuroprotective?

There remains little doubt that injury-induced aromatization in astrocytes and perhaps radial glia, is neuroprotective in mammals and birds. A quick examination of constitutive brain aromatase expression across vertebrate phyla, however, exposes two interesting patterns. Firstly, constitutive neural aromatase expression is extremely high in teleost fish, high in passerine songbirds, and relatively low in mammals. Although it is difficult to directly compare aromatase activities across species, experimental paradigms, and laboratories, (especially given the profound differences in body temperature across the species concerned), the level of aromatase activity in fish and birds is extremely high when compared to the mammalian brain [42,43]. Specifically, in the teleost fish forebrain, aromatase activity levels are 100–1000 times greater than those found in other vertebrates [43,85]. Correspondingly, the distribution of neural aromatase-expressing cells appears to support the idea that brain aromatization is most widespread in teleosts, readily detectable in songbirds, and relatively constrained in mammals. Secondly, while constitutive expression of aromatase is readily detectable in radial glia in teleost fish (some species also express aromatase in neurons [99]) and can be induced by injury in the radial glia of zebra finches [184,84,85,183] it appears exclusively neuronal under normal conditions and astrocytic following injury in the mammalian brain [33]. These observations raise the possibility that constitutive aromatase expression may fit all the three conceptual criteria for neuroprotection (see Section 1), in that the teleost brain may be more plastic and particularly resistant to damage relative to the passerine brain, which, in turn may be more plastic and resilient following damage compared to the brains of mammals. Thus, high levels of neural aromatase may be adaptively linked with continual neurogenesis and robust neuroprotection throughout an organism's lifetime [84,209].

Both fish and birds regularly undergo neurogenesis to produce changes in the brain that subsequently regulate changes in behavior [7,85,128,170]. Aromatization may be key in orchestrating these changes, many of which occur prior to changes in gonadal

tissue [85,37,31]. As previously stated, under normal conditions aromatase is expressed in the radial glia of teleost fish [271,84] and following brain damage in ventricular areas of the songbird brain [184]. Importantly, radial glial cells are neuronal and glial precursors, and are possibly a source of new neurons in fish, birds, and mammals [182,8,283]. In fact, recent observations suggests that neuronal progenitor, radial glia are aromatase positive in the adult zebra fish brain [182]. These data support the idea that adult neural plasticity may be linked with neural aromatase expression across vertebrate phyla. This plasticity may be reflected in the overall level of adult neurogenesis in the brain and/or in the plasticity of neuronal connectivity in the adult brain.

Hippocampal synaptic plasticity may be modulated by local rather than circulating estrogens in mammals, fish and birds [139,104,61,111,2,135,211]. Blocking aromatase activity in hippocampal slices also decreases dendritic spines and synapses in CA1 pyramidal neurons. Importantly, songbirds show a strong relationship between aromatase and hippocampal function [135,211,214,241,187,188]. Yague et al. [272] suggest that a possible role for aromatase in the human brain is to increase local levels of estradiol that mediate synaptic plasticity, thus supporting the role of neural aromatization in synaptic plasticity across vertebrates.

The question that is raised is therefore: If aromatase, estradiol and glial cells provide increased neuronal plasticity and possibly neuroprotection, then evolutionarily why was there a decreased reliance on aromatase activity and plasticity in mammals?

The brains of fish and birds are more plastic than those of humans and most mammals, however, the majority of neuronal plasticity is related to sexually dimorphic behaviors. Teleost fish and songbirds, primarily use aromatase and locally produced estrogens to create sexually dimorphic regions and behaviors, which can change depending on social or seasonal contexts. The most plastic area of the human brain is within the temporal cerebral cortex and, tantalizingly, this is where the some glial aromatase is located and constitutively expressed. It appears that the human and mammalian brain maintained the mechanisms of aromatase and neuronal plasticity, but lost extra-diencephalic areas that needed aromatase and estradiol to produce reproductive signals. One could postulate that humans and most mammals may have evolved a decreased reliance on neurosteroids to produce sexually dimorphic brain regions and behaviors. Birds and fish maintain this sexually dimorphic brain that is regulated more by neurosteroids and aromatase rather than gonadal steroids. In terms of evolution, this decreased reliance on locally produced estrogens (aromatase) in producing sex differences in behavior left the brain more vulnerable to injury and damage.

7. Summary and future considerations

The neuroprotective actions of brain aromatase are relatively well studied in birds and mammals. Aromatase is induced in glia (radial glia and astrocytes) around the site of brain damage. This induction is quite rapid with increases in aromatase detectable 2 h following mechanical damage in the songbird [269]. In rodents and songbirds, locally produced E2 via astrocytic aromatization dramatically decreases apoptotic secondary damage. The inhibitory effect of E2 on apoptosis has been well elucidated in the mammalian model where interactions between peripherally administered E2 and insulin-like growth factor-1 (IGF-1) are key in estrogen-dependent neuroprotection. It is highly likely that this interaction is conserved within the brain where locally produced E2 may interact with IGF-I to affect apoptotic pathways.

There is considerable interest in identifying the factor(s) that upregulate aromatase upon primary damage. Of particular interest to our laboratory are cytokines that are likely released at high levels around the site of primary insult and are well studied for their role in neuro-inflammation. Although the induction of gliosis by neuro-inflammatory processes including the release of cytokines is well studied, whether (or not) this gliosis also includes the induction of aromatase expression in reactive glia remains an open question. These studies are currently ongoing in our laboratory and are crucial in order to understand how glial aromatization is kept quiescent under "normal" conditions, and what about primary neural damage may result in the transcription and translation of the aromatase gene.

Indeed, the molecular mechanism underlying the onset of aromatase transcription in glia remains a mystery. Although we have learned much about aromatase gene structure and regulation in multiple species, the cell-specific regulation of aromatase remains relatively poorly understood. Neural injury and neuroprotection represent two areas of study where pathological phenomena can be used to understand fundamental aspects of neuroendocrine regulation in vertebrates.

Acknowledgements

The Saldanha laboratory is supported by NIH NS 042767. We thank all members of our laboratory and our collaborators for their assistance in conducting several of the experiments described here.

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