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Role of glial cells in the generation of sex differences in neurodegenerative diseases and brain aging

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ABSTRACT

Diseases and aging-associated alterations of the nervous system often show sex-specific characteristics. Glial cells play a major role in the endogenous homeostatic response of neural tissue, and sex differences in the glial transcriptome and function have been described. Therefore, the possible role of these cells in the generation of sex differences in pathological alterations of the nervous system is reviewed here. Studies have shown that glia react to pathological insults with sex-specific neuroprotective and regenerative effects. At least three factors determine this sex-specific response of glia: sex chromosome genes, gonadal hormones and neuroactive steroid hormone metabolites. The sex chromosome complement determines differences in the transcriptional responses in glia after brain injury, while gonadal hormones and their metabolites activate sex-specific neuroprotective mechanisms in these cells. Since the sex-specific neuroprotective and regenerative activity of glial cells causes sex differences in the pathological alterations of the nervous system, glia may represent a relevant target for sex-specific therapeutic interventions.

1. Introduction

In its role as the central coordinator of body homeostasis, the brain must be able to activate selective regulatory mechanisms to cope with the physiological singularities of men and women. Throughout the last decades, numerous investigators have explored the specific anatomical and functional details in the nervous system of males and females that sustain the differences in the central control of reproduction, growth, feeding, metabolism, and other basic body functions (Marrocco and McEwn, 2016; Choleris et al., 2018). In addition to these small and very specific distinctions in the structure and function of the nervous system of males and females, recent evidence suggests that there are also more general sex-specific features in the deterioration of neural tissue with aging and under pathological conditions. Indeed, it has become evident that sex is an essential variable to consider when analyzing the manifestation of neurological, neurodegenerative and psychiatric disorders and in the study of how aging affects sensory systems, motor coordination, systemic homeostasis, spatial orientation and cognition.

Sex differences in the brain are generated by the interaction of short-term and long-term epigenetic actions of gonadal hormones with specific transcriptional products of genes found on the sex chromosomes (Lentini et al., 2013; Cambiasso et al., 2017; Arnold, 2019; Raznahan and Disteche, 2020). Thus, both sex chromosomes and gonadal hormones influence the response of the nervous system and other body tissues to diseases and aging (Ramien et al., 2016; Lee et al., 2019; Caceres et al., 2020; Davis et al., 2020; Gilli et al., 2020), with these two conditions in turn being associated with substantial and sex-specific alterations in the levels and actions of testosterone, estradiol, progesterone and their neuroactive steroid metabolites (Veiga et al., 2004; Melcangi et al., 2016; Giatti et al., 2020b). Clear examples include pregnancy and menopause, which affect the process of brain aging in women (Barth and Lange, 2020; Than et al., 2020; Wang et al., 2020c) and may influence the risk of cognitive decline, dementia and neurodegenerative diseases, such as Alzheimer's disease (Georgakis et al.,

Abbreviations: APOE, apolipoprotein E; APP, amyloid precursor protein; CCL2, chemokine (C-C motif) ligand 2; CNS, central nervous system; DHP, dihydroprogesterone; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; GPER1, G-protein coupled receptor 1; LPS, lipopolysaccharide; PNS, peripheral nervous system; P0, myelin protein zero; PPM22, peripheral myelin protein of 22 KDa; THP, tetrahydroprogesterone, pregnanolone.

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2019; Wang et al., 2020c). Furthermore, it is important to consider that sex differences in the brain's response to pathology and aging depend not only on the inherent structural and functional sexual dimorphisms in the nervous system or on the sex specific actions of gonadal hormones and their metabolites on brain cells, but they also depend on sex differences in systemic functions. Indeed, there are sex differences in systemic immunity, metabolism and cardiovascular function caused by hormones and sex chromosomes, which can also contribute to the generation of male and female specific responses of the nervous system to physiological and pathological challenges (Ramien et al., 2016; McCarthy and Raval, 2020; Barnes and Charkoudian, 2021). For instance, metabolic factors can contribute to sex differences in brain aging and although higher body mass index is associated with greater brain deterioration with aging in humans, this association is stronger in men than in women (Armstrong et al., 2019; Alqarni et al., 2020; Chin Fatt et al., 2020). The degeneration or malfunctioning of neurons is the most obvious cause of the cognitive, affective, and behavioral deficits associated to brain disorders and aging, with sex-specific modifications in neurons (McEwen, 2002; Richetin et al., 2017; Giacobini and Pepeu, 2018; Arsenault et al., 2020) possibly explaining some of the differences between males and females in brain deterioration associated to pathology and aging. However, the focus of the present analysis will be on the role played by another cellular component of the nervous system in this sex-specific deterioration: the glial cells.

There are various relevant reasons that the role of glial cells in the generation of sex differences in neurodegenerative diseases and brain aging must be considered. First, the survival and function of neurons are directly associated to their surrounding glial environment and depend on a multitude of trophic and neuromodulatory signals released by glia. In addition, glial cells are essential components in the degenerative, protective and reparative responses of the nervous system to pathological insults; they are affected by aging and, as recent evidence indicates, they present marked sexual dimorphisms and are direct targets for the actions of gonadal hormones and sex-linked genes in the brain. Therefore, in the following sections we will discuss how glial cells may play a major role in the generation of sex differences in the deficits in brain function caused by pathology and aging.

2. Glial cells

2.1. Cell types and functions

The term glia includes a heterogeneous group of cell types with a variety of functions. The best characterized glial cells are the astrocytes, oligodendrocytes and microglia in the central nervous system (CNS) and the Schwann cells in the peripheral nervous system (PNS). Other specialized glial cells include tanycytes in the hypothalamus (Rodríguez et al., 2019) and Bergmann glia in the cerebellum. In addition, the more recently identified NG2 cells are generally considered to be an additional glial cell type in the CNS that also acts as progenitors for astrocytes and oligodendrocytes and possibly for neurons.

Although the basis of the modern classification of glial cell types was completed following the work of Río-Hortega at the beginning of the XX century (Pérez-Cerdá et al., 2015; Sierra et al., 2019; Boullerne and Feinstein, 2020), our knowledge concerning the role of glia has considerably benefited by a revival of the interest in these cells initiated about 25 years ago. The resulting research has brought about the recognition of glial cells as indispensable players in the functional activity of the nervous system, not only by maintaining neuronal homeostasis and metabolism, but also by communicating with neurons through different molecular mechanisms to control information processing (Masgrau et al., 2017).

In the CNS, oligodendrocytes insulate axons and provide them with trophic support, regulating their development, maintenance, repair and plasticity. In addition, oligodendrocyte plasma membranes are the main component of myelin, a structure that allows long-distance fast saltatory conduction of neuronal impulses and is indispensable for the functional activity of the CNS, including cognition (Serrano-Regal et al., 2020; Xin and Chan, 2020). Schwann cells in the PNS exert the function of oligodendrocytes in the CNS, myelinating peripheral axons and participating in the maintenance and regeneration of peripheral nerves (Bolívar et al., 2020).

Astrocytes regulate neuronal development, synaptic plasticity, neurotransmission and myelin formation and participate in conjunction with microglia to maintain the local immune response in the CNS (Ferrer, 2017; Mederos et al., 2018; Augusto-Oliveira et al., 2020; Bernaus et al., 2020). In addition, astrocytes control the blood brain barrier (Cabezas et al., 2014) and are essential for the maintenance of neuronal metabolism by providing lactate to neurons and adapting the cerebral blood flow and the extracellular concentration of water and ions to the changes in neuronal activity (Pellerin et al., 2007; Attwell et al., 2010; Bolaños, 2016; Takahashi, 2020). Furthermore, astrocytes are sensitive to systemic and central metabolic signals and those located in the hypothalamus regulate, together with microglia (Dorfman et al., 2017), the activity of neurons involved in body metabolic homeostasis (Freire-Regatillo et al., 2017; Chowen et al., 2019).

In contrast to the other glial cell types, microglia have a mesodermal origin and have been classically considered as the macrophages of the CNS. Indeed, although different from macrophages, these cells actively participate in the local immune reaction in response to infections or pathological insults (Bernaus et al., 2020; Rodríguez-Gómez et al., 2020) and release reparative factors into the injured tissue (Nakajima and Kohsaka, 2004; Sohrabji and Williams, 2013; Villa et al., 2019). As reported for macrophages, microglia adopt a variety of phenotypes with different pro-inflammatory or immunosuppressive activites (Morganti et al., 2016; Ransohoff, 2016; Tang and Le, 2016). Moreover, they exert other important basic physiological functions by controlling developmental and adult neurogenesis, apoptosis, synaptic pruning, and the plastic remodeling of neuronal circuits (Sierra et al., 2010; Weinhard et al., 2018a; Sirerol-Piquer et al., 2019; Diaz-Aparicio et al., 2020).

2.2. Glial cells under pathological conditions

As active monitors of the homeostasis and activity of the nervous system, glial cells are involved in the defense of nervous tissue from injury and in the mechanisms of repair and regeneration (Boghdadi et al., 2020; Cooper et al., 2020; Linnerbauer and Rothhammer, 2020; Zhou et al., 2020; Zamboni et al., 2020; Dos Santos et al., 2021). In consequence, inherent pathological alterations in these cells or the collapse of their protective mechanisms when confronted with uncontrollable degenerative stimuli might also contribute to the etiology or the manifestation of neurological (Ferrer, 2017; Bae et al., 2020; Zimmer et al., 2020), neurodegenerative (Ferrer, 2017; Sidoryk-Węgrzynowicz et al., 2019; Garcia et al., 2020; Guo et al., 2020; Habib et al., 2020; Udovin et al., 2020), psychiatric (Raabe et al., 2019; Zuccoli et al., 2019) and cognitive (Santello et al., 2019) disorders and to the pathogenesis of chronic pain (Donnelly et al., 2020).

This dual role of glial cells as promoters or repressors of the pathological alterations often makes the interpretation of their changes in response to a pathological insult difficult. In addition, the existence of a considerable variety of subtypes of astrocytes, oligodendrocytes and microglia that may respond heterogeneously to the pathological insults (Masgrau et al., 2017; Mrdjen et al., 2018; Stratoulias et al., 2019) is now becoming evident. Recent analyses of the different phenotypes that glial cells adopt in response to brain injury are facilitating the identification of the molecular characteristics of these cells that determine their protective or damaging contribution to tissue homeostasis in the injured brain (Zamanian et al., 2012; Bonham et al., 2019; Afridi et al., 2020; Johnson et al., 2020; Nathalie et al., 2020).

2.3. Glial cells in the aging brain

Glial cells show phenotypic modifications during aging (Salas et al., 2020). Although some of these modifications may represent functional adaptions, there is evidence that glial cells, in particular astrocytes and microglia, acquire dysfunctional phenotypes in the aged brain that decrease their capacity to maintain homeostasis (Sierra et al., 2007). Thus, aged glial cells are not capable of adequately regulating extracellular glutamate levels (Limbad et al., 2020) or of effectively clearing both intracellular and extracellular debris (Njie et al., 2012; Gordleeva et al., 2020; Marschallinger et al., 2020; Valenza et al., 2020; Yanguas-Casás et al., 2020). This renders them less capable of providing functional support to neurons and myelin (Neumann et al., 2019; Wang et al., 2020a), of maintaining the functional integrity of the blood brain barrier (Popescu et al., 2009; Ferrer, 2017) and of mounting an adequate protective response to injury (Early et al., 2020). These functional alterations in aged glial cells contribute to the deterioration of the neural tissue in older individuals. In addition, since hypothalamic glial cells are involved in the neuroendocrine control of systemic homeostasis, their modifications with aging may also contribute to the deterioration of other body tissues (Chowen and Garcia-Segura, 2020).

3. Sex differences in brain alterations with pathology and aging

Numerous pathological alterations of the nervous system present specific features in men and women. Thus, the incidence, prevalence, age of onset, pathophysiology and symptomatology of the illness, or even in some cases its response to therapeutic interventions, may be different in males and females. For instance, autism is predominantly a male disorder (Ferri et al., 2018). The incidence and prevalence of Parkinson's disease is also greater in men than in women (Jurado-Coronel et al., 2018; Meoni et al., 2020). Younger men also have a higher incidence of stroke compared to younger women (Roy-O'Reilly and McCullough, 2018; Jiang et al., 2020). In contrast, women are at higher risk for posttraumatic stress disorder (Kornfield et al., 2018) and depression is more frequently diagnosed in this sex (Eid et al., 2019). Women have also higher prevalence and incidence of Alzheimer's disease (Fisher et al., 2018; Dubal, 2020) and higher incidence of multiple sclerosis and a higher relapse frequency than men, although the course of the disease is more benign in women (Schwendimann and Alekseeva, 2007; Kalincik et al., 2013). Sex differences have also been detected in diabetic encephalopathy (Melcangi et al., 2016), essential tremor, Huntington disease (Meoni et al., 2020), traumatic brain injury (Gupte et al., 2019) and epilepsy (Christian et al., 2020), among other pathologies of the nervous system.

Differences in brain deterioration with aging between men and women have also been reported. For instance, brain imaging studies have revealed sex-specific regional differences in the rate of volume decline of the gray and white matter with aging, with men having greater global brain volume loss over time than women (Armstrong et al., 2019). Men also experience an earlier decline in white matter microstructure than women (Toschi et al., 2020). In addition, sex differences in brain aging may affect the risk of brain illnesses, as for instance, the risk of Alzheimer's disease is similar in men and women at young ages. However, older women are at higher risk than older men to develop this pathology (Dubal, 2020). The incidence of stroke is also higher in older women compared to older men, in contrast to the situation at younger ages when men are at higher risk than women (Roy--O'Reilly and McCullough, 2018; Jiang et al., 2020).

4. Contribution of glial cells to the generation of sex differences in brain pathology and aging

4.1. Oligodendrocyte precursors, oligodendrocytes and myelin

Male rats and mice show higher densities of oligodendrocytes in the corpus callosum, fornix and the ventral funiculus of the spinal cord compared to females. This is associated with a greater thickness of myelin sheaths and higher expression of some myelin proteins in males and to a shorter lifespan of female oligodendrocytes (Cerghet et al., 2006, 2009). These differences emerge during the first 10 postnatal days of life and are dependent on perinatal androgens acting through androgen receptors (Abi Ghanem et al., 2017). Sex differences in oligodendrocytes may contribute to the reported differences in the myelination of the corpus callosum in male and female rodents (Moore et al., 2013) and to sex differences detected in the volume of some white matter tracts in the human brain (Sacher et al., 2013), although it is evident that other cellular components in addition to oligodendrocytes contribute to the determination of white matter volume.

Sex differences in oligodendrocytes could affect the way they respond to pathological conditions and could therefore contribute to the different manifestations of brain illnesses in males and females. For instance, it has been reported that male and female oligodendrocytes present different transcriptional signatures in Alzheimer's disease. In a single cell transcriptome study of postmortem prefrontal cortex samples from human subjects with Alzheimer's disease, oligodendrocytes and neurons were the two cell types showing a greater sex divergence in transcriptional modifications in response to the pathology, with increased pathology correlating with a global transcriptional activation in male oligodendrocytes that was not detected in female oligodendrocytes (Mathys et al., 2019). These differences in the response of male and female oligodendrocytes may contribute to sex differences in the pathological alterations of the white matter in Alzheimer's disease and, therefore, to sex differences in the cognitive consequences of the disease.

Oligodendrocytes are generated from oligodendrocyte precursor cells that persist during adult life and generate new mature oligodendrocytes that participate in myelin remodeling, myelin repair and remyelination in the adult brain (Young et al., 2013). Transcriptomic analyses of oligodendrocyte precursor cells have also identified sex differences in the expression of genes encoding for proteins involved in cell cycle, proliferation, maturation and myelination, among other functions (Yasuda et al., 2020). In addition, in the previously mentioned single cell transcriptome study of the prefrontal cortex from human subjects with Alzheimer's disease, female oligodendrocyte precursors showed a down-regulation shift in response to pathology that was not observed in male cells (Mathys et al., 2019).

Transcriptional differences in male and female oligodendrocyte precursor cells are reflected in different functional properties of these cells. For example, female oligodendrocyte precursors are more proliferative (Cerghet et al., 2006; Yasuda et al., 2020), have a greater migratory ability (Yasuda et al., 2020) and are more resistant to *in vitro* ischemia and oxidative stress (Sunny et al., 2020; Yasuda et al., 2020) compared to male oligodendrocyte precursors. In contrast, male oligodendrocyte precursors have higher differentiation and myelinating activities (Cerghet et al., 2006; Yasuda et al., 2020). These functional sex differences of oligodendrocyte precursors may confer some advantages to females over males in some aspects of the remyelination process. Indeed, in a model of demyelination induced by the stereotaxic injection of ethidium bromide in the caudal cerebellar peduncles, Li et al. (2006) detected significantly greater remyelination in older adult (12 months old) female rats compared to age-matched males at 8 weeks after lesion induction. In contrast, young male and female rats showed the same degree of remyelination in the same experimental model (Li et al., 2006), suggesting that sex difference in remyelination only become apparent during the slower rate of remyelination that occurs in older animals, when oligodendrocyte precursor recruitment and differentiation may be compromised (Sim et al., 2002).

4.2. Astrocytes

Numerous studies have detected physiological sex differences in the number, morphology, gene expression and function of astrocytes in

different regions of the developing and adult CNS (Beyer et al., 1990; Chowen et al., 1995; Amateau and McCarthy, 2002; Arias et al., 2009; Acaz-Fonseca et al., 2016). In addition, male and female astrocytes show divergent reactive changes in response to pathological insults, including *in vitro* exposure to bacterial lipopolysaccharide (LPS) (Santos-Galindo et al., 2011; Loram et al., 2012; Chistyakov et al., 2018), toxins (Astiz et al., 2014), ethanol (Wilhelm et al., 2016) or oxygen-glucose deprivation (Liu et al. 2007). Male and female astrocytes also show differences in their response to different *in vivo* manipulations in animal models of neonatal hypoxia-ischemia (Morken et al., 2014), stroke (Morrison and Filosa, 2016), traumatic brain injury (Acaz-Fonseca et al., 2015), Parkinson's disease (Mitra et al., 2015) or experimental autoimmune encephalomyelitis (Tassoni et al., 2019). Moreover, sex differences in the response of astrocytes are also detected after the exposure to psychosocial challenges, such as prenatal stress (García-Cáceres et al., 2010) or maternal deprivation (López-Gallardo et al., 2012).

The response of astrocytes to pathological insults may play a major role in the way that male and female brains cope with neurodegenerative alterations. Since neuroinflammation and oxidative stress are common conditions in most neurodegenerative diseases, it is of great relevance that male and female astrocytes show differential expression of inflammatory genes in response to inflammatory challenges (Santos-Galindo et al., 2011; Loram et al., 2012; Chistyakov et al., 2018) or after the *in vivo* or *in vitro* exposure to conditions that increase cellular oxidative stress (Astiz et al., 2014; Wilhelm et al., 2016). Sex differences have also been reported after *in vivo* cortical injuries in the expression of chemokine (C-C motif) ligand 2 (CCL2), which is involved in the recruitment of immune cells and the regulation of gliosis (Acaz-Fonseca et al., 2015). These different gene responses may in part reflect specific strategies of male and female astrocytes to recover tissue homeostasis. In this regard, an interesting observation is that inflammation *in vitro* stimulates phagocytosis of brain-derived cellular debris by male astrocytes but inhibits phagocytosis activity in female astrocytes (Crespo-Castrillo et al., 2020), suggesting sex specific differences in the role played by these cells to reestablish tissue homoeostasis. However, their divergent responses may also reflect differences in their vulnerability to pathological insults. For instance, ethanol exposure *in vivo* and *in vitro* seems to induce a dysfunctional phenotype in female astrocytes that is not observed in male astrocytes (Wilhelm et al., 2016). In contrast, female astrocytes in primary cultures from newborn rats are more resistant to oxygen-glucose deprivation-induced cell death than male astrocytes (Liu et al., 2007).

The greater resistance of female neonatal astrocytes to *in vitro* oxygen-glucose deprivation suggests that they have a better metabolic adaption response to this insult. In agreement with this, female astrocytes show enhanced mitochondrial metabolism immediately after *in vivo* neonatal hypoxia-ischemia compared to male astrocytes (Morken et al., 2014). However, male astrocytes show a faster recovery from the neonatal injury (Morken et al., 2014). Since astrocyte metabolism supports the metabolic activity of neurons, these sex differences in the metabolic response of astrocytes after CNS injury could result in a difference in neuronal damage in male and female neurons. Astrocyte metabolism is coordinated through transient intercellular Ca^{2+} waves, which are also essential for proper neuron-astrocyte communication and for adaptation of the metabolic coupling between astrocytes and neurons in response to metabolic insults (Ding, 2014). In this regard, it is important to note that immediately following middle cerebral artery occlusion in adult mice, astrocytes in the ipsilateral hemisphere of females respond with a higher frequency of Ca^{2+} elevations compared to males (Morrison and Filosa, 2016). However, the functional significance of this sex difference is still unclear.

Another important aspect concerning astrocytes is their contribution to the generation of sex differences in the neuroendocrine control of metabolism (Chowen et al., 2018). Male and female hypothalamic astrocytes are differentially affected by systemic metabolic challenges (Argente-Arizón et al., 2018) and could thus be involved in the difference between the sexes in the onset of obesity-related pathologies, which in turn produces systemic changes that can impact on the brain generating a vicious circle that modifies the neurodegenerative alterations in neurological diseases and the process of brain aging (Chowen and Garcia-Segura, 2020).

4.3. Microglia

Studies have characterized sex-specific aspects in microglia gene expression (Guneykaya et al., 2018; Hanamsagar et al., 2017; Thion et al., 2018; Villa et al., 2018), miRNA levels (Kodama et al., 2020), cell number (Mouton et al., 2002; Schwarz et al., 2012; Lenz et al., 2013; Thion et al., 2018) and morphology (Lenz et al., 2013) that could influence brain development and function under physiological conditions and may also impact on the response of injured neural tissue to pathological alterations. During development, microglia contribute to the shaping of neuronal circuits and synaptic connections. Thus, sex differences in the pattern of colonization of the developing brain by microglia (Schwarz et al., 2012), together with sexually dimorphic responses of these cells to the action of environmental factors during this period, could contribute to the generation of sex differences in neurodevelopmental disorders (Bordeleau et al., 2019; Nelson et al., 2019) and to the response of the nervous system to neonatal injury (Villapol et al., 2019). In adult life, sex differences in microglia may determine the neural response to pathological insults. Indeed, microglia show sexually dimorphic responses after brain injury in the adult brain as shown in animal models of traumatic brain injury (Acaz-Fonseca et al., 2015; Caplan et al., 2017; Villapol et al., 2017), ischemic stroke (Morrison and Filosa, 2016; Villa et al., 2018; Kerr et al., 2019; Rahimian et al., 2019) and acute inflammation induced by the administration of LPS (Hanamsagar et al., 2017). The microglial inflammatory response might also be involved in sex differences in depressive behavior (Liu et al., 2019).

The divergent activation of male and female microglia under pathological conditions may be secondary to overall sex differences in the manifestation of the disease, but it could also reflect intrinsic differences in the cellular mechanisms to cope with brain damage. Indeed, studies in which female microglia were transplanted to the brain of male mice subjected to focal cerebral ischemia have shown that microglia contribute to determine sex differences in the outcome of the brain lesion (Villa et al., 2018). Female microglia transplants have positive effects in male injuries while male microglia transplants do not ameliorate injuries in the female brain. Therefore, endogenous differences in the protective and reparative actions of male and female microglia contribute to the generation of sex differences in brain pathology in this animal model. Indeed, sex influences several basic responses of microglia to stimulation that are essential for their protective and reparative actions, such as migration (Yanguas-Casás et al., 2018), phagocytosis (Nelson et al., 2017; Weinhard et al., 2018b; Yanguas-Casás et al., 2018, 2020) and neuroimmune responses (Osborne et al., 2018).

In addition to sex, another factor that influences microglia gene expression and their reaction to stimulation is aging (Mangold et al., 2017; Sierra et al., 2007; Osborne et al., 2018; Bonham et al., 2019; Yanguas-Casás et al., 2020). Moreover, sex differences in microglia gene expression with aging have been detected in the mouse hippocampus and cerebral cortex. These studies revealed that in older brains microglia have higher expression of inflammation-related transcripts in females compared to males (Mangold et al., 2017). In addition, single-cell RNA-sequencing analysis in the brain of amyloid precursor protein (APP) transgenic mice has revealed divergences in gene expression of male and female microglia in response to progressive β-amyloid deposition (Sala Frigerio et al., 2019), a situation that occurs both with aging and in Alzheimer's disease. Furthermore, in mice with the apolipoprotein E (APOE) 3 genotype, microglia respond to β-amyloid deposition with a greater coverage of β-amyloid plaques in males than in females

(Stephen et al., 2019). There is also evidence that sex differences in microglia microRNAs contribute to sex differences in tau pathogenesis (Kodama et al., 2020). In this regard, it is important to mention that tauopathy, amyloidosis and aging have been shown to share a common APOE-driven transcriptional signature in microglia (Kang et al., 2018). Interestingly, female microglia show increased expression of many of these transcripts in older mouse brains (Kang et al., 2018), which may be related with increased susceptibility to Alzheimer's disease in females. Finally, functional studies analyzing microglial Ca^{2+} signaling and process motility indicate more rapid aging of microglia in female mice (Olmedillas Del Moral et al., 2020). Taken altogether, the above studies suggest that microglia may also contribute to sex differences in brain vulnerability to neurodegenerative diseases at older ages.

5. Influence of gonad-independent effects of sex chromosomes in the response of glial cells to the pathological alterations of the nervous system

An obvious example of sex-specific diseases of the nervous system are those caused by mutations of genes localized on the X or Y chromosomes. When these genes are localized on the male-specific region of the Y chromosome, the disease is male-specific (Jangravi et al., 2013). In general X-linked diseases also have a stronger phenotype in men than in women (Migeon, 2020). X-linked neurological diseases include Charcot-Marie-Tooth disease, Pelizaeus-Merzbacher Disease, Rett syndrome, X-linked adrenoleukodystrophy and X-linked intellectual disability, among others.

In addition, sex chromosome genes could influence the manifestation of other neurodegenerative diseases, such as Alzheimer's disease (Caceres et al., 2020; Davis et al., 2020), Parkinson's disease (Lee et al., 2019), stroke (McCullough et al., 2016) and multiple sclerosis (Ramien et al., 2016; Gilli et al., 2020). Adding a second X chromosome to XY males or XX females decreases mortality and cognitive deficits in a mouse model of Alzheimer's disease (Davis et al., 2020). In contrast, compared to the XY complement, the XX complement increases the susceptibility of mice to develop experimental autoimmune encephalomyelitis, a model of multiple sclerosis (Ramien et al., 2016; Gilli et al., 2020), and results in increased infarct volume in a model of stroke in aged mice (McCullough et al., 2016).

Most of the effects of XY and XX complements can be attributable to genes localized on the X chromosome. It is well known that the expression dosage of X chromosome genes in XX and XY complements is compensated for in mammals by silencing transcription from one of the two X chromosomes of females. However, X chromosome inactivation is not complete, and in humans it has been estimated that incomplete inactivation affects at least 23 % of X chromosome genes (Tukiainen et al., 2017) and varies from cell to cell, among tissues and between individuals. The brain is not an exception and numerous X chromosome genes escape inactivation in the human brain, resulting in sex biases in gene expression by neurons and glial cells.

Genes of the Y chromosome may also contribute to gonad-independent sex-specific effects of the XX and XY complements. It has been reported that extreme downregulation of the Y chromosome in the human brain increases the aged-related risk of Alzheimer's disease (Caceres et al., 2020), suggesting that the Y chromosome offers resilience to the disease. One of the most interesting Y chromosome genes is *sry*, which initiates testis formation during development and causes masculinization in mammals. This gene continues to be expressed in adult tissues, including the brain, and exerts gonad-independent functions. For instance, *sry* contributes to the regulation of dopamine biosynthesis and motor function under physiological conditions during adulthood (Dewing et al., 2006; Wu et al., 2009; Czech et al., 2012). However, *sry* is aberrantly upregulated in human cell models of Parkinson's disease as well as in the substantia nigra of male rats treated with 6-hydroxydopamine, an experimental model of the disease. Interestingly, silencing of *sry* in the substantia nigra of male rats decreases mitochondrial dysfunction, neuroinflammation, dopaminergic cell loss and motor deficits in the 6-hydroxydopamine model (Lee et al., 2019).

All these findings suggest that genes on the sex chromosomes may contribute to generate sex differences in brain pathology. Although further investigation is needed to clarify the precise role of glial cells in many of these sex chromosomes effects, it is interesting to note that the XX complement results in a higher level of microglia activation after stroke in aged mice compared to the XY complement (McCullough et al., 2016). This suggests that sex chromosome complement may contribute to the generation of a sexually dimorphic immune response mediated by microglia. In addition, glial cells are involved or play a major role in the neurological phenotype of numerous X-linked diseases, such as Schwann cells in Charcot-Marie-Tooth disease (Murakami and Sunada, 2019), oligodendrocytes in Pelizaeus-Merzbacher Disease (Nevin et al., 2017; Inoue, 2019) and Rett syndrome (Kahanovitch et al., 2019), astrocytes in X-linked intellectual disability (Pillet et al., 2020) and astrocytes and microglia in Rett syndrome (Zhao et al., 2017; Kahanovitch et al., 2019) and cerebral X-linked adrenoleukodystrophy (Görtz et al., 2018; Bergner et al., 2019).

6. Glial cells as mediators of sex-specific neuroprotective actions of gonadal hormones

In contrast to the limited knowledge regarding the role of glial cells in mediating the gonad-independent actions of sex chromosomes on brain pathology, there is abundant evidence that these cells participate in the regulation exerted by gonadal hormones on injured nervous tissue (Garcia-Segura and Melcangi, 2006). Most of these hormonal effects are neuroprotective and reparative and contribute to the generation of sex-specific modulation of the injured and aged brains (Azcoitia et al., 2019; Gölz et al., 2019; Altaee and Gibson, 2020). Gonadal hormones are steroids derived from cholesterol. Part of their effects in the nervous system are exerted through their neuroactive steroid metabolites, which, like to the hormones from which they are derived, are present at different levels in the nervous tissue of males and females (Melcangi et al., 2016; Giatti et al., 2019), react with sex-specific changes to neural injury and brain pathology (Mirzatoni et al., 2010; Melcangi et al., 2016; Zhu et al., 2017; Akwa, 2020; Giatti et al., 2020c) and are modified with aging (Schumacher et al., 2003; Vallée et al., 2004; Caruso et al., 2013).

Schwann cells, oligodendrocytes, astrocytes and microglia actively participate in the generation of neuroactive steroid metabolites (Zwain and Yen, 1999; Garcia-Segura and Melcangi, 2006; Karri et al., 2007; Chen et al., 2014; Wicher and Norlin, 2015; Giatti et al., 2020a). These glial derived steroids can generate different responses in the nervous system of males and females. For instance, neuroactive progesterone and androgen metabolites produced by Schwann cells and oligodendrocytes participate in sex-specific effects on myelin formation and repair in the PNS and CNS, respectively (Giatti et al., 2020a), affecting the outcome of peripheral neuropathies and central demyelinating diseases. Likewise, the metabolism of testosterone by astrocytes after brain injury (Garcia-Segura et al., 1999; Saldanha et al., 2013) exerts sex-specific neuroprotective actions (Liu et al., 2007; Chisholm and Sohrabji, 2016; Saldanha, 2020) by increasing the local levels of neuroprotective estradiol in the damaged neural tissue (Chen et al., 2007; Mehos et al., 2016; Wang et al., 2020b).

Glial cells are also directly targeted by gonadal hormones and their metabolites, since they express androgen receptor (DonCarlos et al., 2006), estrogen receptor (ER) α, ERβ, G-protein coupled ER (GPER) 1 (Acaz-Fonseca et al., 2016; Marraudino et al., 2020), a variety of progesterone receptors (Castelnovo et al., 2019) and non-classical steroid receptors, such as the GABA-A receptor (Melcangi et al., 2005). In addition, the expression of steroid receptors by glia is in general enhanced under neuroinflammatory (Liu et al., 2005) and neurodegenerative (Acaz-Fonseca et al., 2014) conditions, such as those occurring after different forms of mechanical and traumatic brain injury (Blurton-Jones and Tuszynski, 2001; García-Ovejero et al., 2002;

Duncan et al., 2013; Meffre et al., 2013), ischemic injury (Zhang et al., 2018), Alzheimer's disease (Lu et al., 2003), or amyotrophic lateral sclerosis (McLeod et al., 2020). Therefore, glial cells are direct targets of the actions of gonadal hormones and their metabolites in the injured brain where they modulate reactive gliosis and the glial control of immune responses, neural metabolism, the extracellular milieu, axonal regeneration, remyelination, the neurovascular unit and the blood brain barrier, contributing to the maintenance of tissue homeostasis of the brain and the spinal cord under acute (Feeser and Loria, 2011; Johann and Beyer, 2013) and chronic (Arevalo et al., 2013; Kipp et al., 2016) pathological conditions.

Since the circulating and local levels of gonadal hormones and their metabolites are different in adult males and females and present a sex-specific decline with aging (Melcangi et al., 1998; Chisholm and Sohrabji, 2016; Kerr et al., 2019; Rahimian et al., 2019; Acosta-Martínez, 2020), the regulation that they exert on glial cells is logically also different depending on sex and age. Furthermore, gonadal hormones also induce sex differences in glial cell function because the same hormone activates different signaling mechanisms and generates different cellular responses in male and female glial cells (Acaz-Fonseca et al., 2016; Frago et al., 2017; Stary et al., 2017; Bollinger et al., 2019; Acosta-Martínez, 2020). A clear example of this is that male and female glia show divergent changes in the expression of gonadal hormone receptors and steroidogenic enzymes under pathological conditions (Liu et al., 2007; Astiz et al., 2014; Luchetti et al., 2014; Ortiz-Rodriguez et al., 2019; Pan et al., 2020) and this results in sex-specific neuroreparative and neuroprotective actions of gonadal hormones and their metabolites.

There are numerous examples of sex-specific differences in the actions of gonadal hormones on central and peripheral glia. In the PNS, estradiol and progesterone regulate Schwann cell proliferation, which is essential for the maintenance, regeneration and remyelination of peripheral nerves. However, estradiol promotes Schwann cell proliferation in the peripheral nerves of males, but not in females. In contrast, progesterone promotes Schwann cell proliferation in females but has little effect on male nerves (Fex Svenningsen and Kanje, 1999). Progesterone and its reduced metabolites also induce sex-specific regulation of myelin proteins in Schwann cells, as progesterone increases the expression of the genes encoding myelin protein zero (P0) and peripheral myelin protein of 22 KDa (PMP22) in male but not in female Schwann cells. The metabolite of progesterone, dihydroprogesterone (DHP), has the same effect as progesterone on P0, increasing its expression in male but not in female cells. However, DHP was not shown to affect the expression of PMP22. In contrast, another progesterone metabolite, tetrahydroprogesterone (THP), increases the expression of both P0 and PMP22 in female Schwann cells but not in male cells and increases the gene expression of another myelin protein, MAG, only in male cells (Magnaghi et al., 2006). These differences in the effects of progesterone and its metabolites may be explained by their differential affinity to the variety of classical and non-classical progesterone receptors expressed in Schwann cells (Castelnovo et al., 2019).

Sex-specific actions of gonadal hormones on central glia have also been reported. This is the case of testosterone that, when acting during the specific critical developmental periods for brain sexual differentiation, generates long-lasting differences in male and female oligodendrocytes (Abi Ghanem et al., 2017), astrocytes (Chowen et al., 1995; Garcia-Segura et al., 1988) and microglia (Lenz et al., 2013). In addition, testosterone exerts different actions on male and female glia during adult life. For instance, it has been reported that testosterone affects astrocyte number and morphology in the medial amygdala of male rats but exerts minimal changes in the morphology of medial amygdala astrocytes in females (Johnson et al., 2012). These actions of testosterone on glia may be mediated by glial androgen receptors (Garcia-Ovejero et al., 2005; DonCarlos et al., 2006), or could be indirect after its conversion to metabolites, such as estradiol or 3α-diol, with affinity for glial ERs (Garcia-Segura and Melcangi, 2006). Indeed, estradiol, in addition to being a gonadal hormone, is a metabolite of testosterone produced in the brain of both sexes. Therefore, estradiol acts on both male and female glial cells, but its actions are not always identical in males and females. For instance, in the female hypothalamus, estradiol induces the synthesis of progesterone by astrocytes as a mechanism involved in the positive feed-back produced by estrogen that is necessary for ovulation. This is a sex-specific response, since this hormone does not stimulate progesterone synthesis in male rat hypothalamic astrocytes (Kuo et al., 2010). The difference may be related with the inability of estradiol to translocate ERα to the plasma membrane in male astrocytes (Kuo et al., 2010). Sex differences in ER signaling may also be involved in the differential regulation of glycogen metabolism observed in male and female hypothalamic astrocytes in response to this hormone (Ibrahim et al., 2020), which also activates different ER signaling mechanisms in male and female hippocampal astrocytes exposed to a strong metabolic challenge, such as palmitic acid (Frago et al., 2017).

Sex differences in the effect of estradiol on astrocyte metabolism may be highly relevant in conditions of brain injury when astrocyte metabolism is essential to maintain neuronal function in the damaged tissue. In response to brain injury astrocytes also increase their proliferation to recover tissue homeostasis and this process is also regulated by gonadal hormones (Garcia-Estrada et al., 1993). Studies in primary mouse cortical astrocytes have shown that the regulation of astrocyte proliferation by estradiol is different in males and females, with this hormone increasing proliferation in female, but not in male astrocytes (Arnold et al., 2008). According to another study, sex differences in estradiol-induced cell proliferation of cortical astrocytes could be due to a stronger inhibition of extracellular signal-regulated kinase (ERK) signaling in female cells by this hormone (Zhang et al., 2002). Progesterone also induces sex differences in astrocyte proliferation, increasing astrocyte cell number in female cultures but decreasing it in male cultures (Arnold et al., 2008).

Together with astrocyte proliferation, another important glial response after brain injury is the regulation of neuroinflammation, which is mainly driven by microglia and is also known to be regulated by gonadal hormones. In a model of traumatic brain injury in rats, the selective GPER1 agonist G1 was shown to exert anti-inflammatory effects and to reduce microglia reactive polarization in the cerebral cortex of males and ovariectomized females, but not in the cortex of intact females (Pan et al., 2020). Therefore, estradiol signaling through GPER1 may have a different effect on microglia activation in males and females after brain injury.

As mentioned before, microglia activation is altered with aging and this could reduce their ability to cope with neurodegenerative challenges. The effect of aging and estradiol on microglia activation has been studied using stimulation with LPS, a classical manner to activate microglia *in vitro*. Using this model Loram et al. (2012) demonstrated that estradiol exerts anti-inflammatory effects in male microglia isolated from the neonatal hippocampus and exposed to LPS but increases the pro-inflammatory response of neonatal female microglia. In contrast, when microglia are isolated from adult hippocampus, estradiol significantly reduces interleukin 1β expression in female, but not in male cells (Loram et al., 2012). These findings suggest that this hormone has different effects in the neuroinflammatory response of microglia depending not only on sex but also on age, although the response of microglia isolated from older animals was not analyzed in this study.

Sex differences in the action of gonadal hormones on glial cells have different therapeutic implications. For instance, some synthetic steroids with affinity for gonadal hormone receptors are used in clinical practice and some of them exert neuroprotective actions and target glial cells (Arevalo et al., 2012). These molecules might also have different effects in male and female glia and could therefore have different therapeutic results when applied to men and women. For example, the synthetic steroid tibolone, used for the treatment of menopausal symptoms (Del Río et al., 2020), stimulates phagocytosis of cellular debris by primary astrocytes in both sexes, but its effect is significantly greater in female

cells. In addition, the mechanisms of action of tibolone to stimulate phagocytosis involves different sets of receptors in male and female cells (Crespo-Castrillo et al., 2020). Furthermore, under basal conditions estradiol synthesized by male astrocytes inhibits the effect of tibolone on phagocytosis, while estradiol produced by female astrocytes stimulates the effect of tibolone on phagocytosis. The situation is different under inflammatory conditions when estradiol synthesis by astrocytes potentiates the effect of tibolone on phagocytosis in both male and female cells with, however, the effect being more pronounced in females (Crespo-Castrillo et al., 2020).

These findings illustrate several interesting sex differences in the effects of synthetic steroids on glia: (i) Synthetic steroids, such as tibolone, may have different effects in male and female glial cells; (ii) The effect of synthetic steroids on glia is differentially affected by local steroids produced by male and female glial cells and (iii) The interaction of synthetic steroids, natural steroids and sex on glial cells is different under physiological conditions than under an inflammatory challenge. These different glial responses to synthetic steroids need to be considered when using these molecules for therapeutic treatments.

7. Conclusions

Evidence of differences between men and women in the onset, progression, outcome, and treatment of diseases has accumulated in recent years, raising the demand for sex and gender-specific medicine. Accordingly, the consideration of sex as a variable has progressively increased in basic research and biomedical studies. Age *per se* is also a variable that often interacts with sex in the manifestation of pathological alterations of the nervous system. Indeed, being elderly is an important risk factor for numerous neurodegenerative alterations. Thus, the incidence of neurodegenerative diseases and the associated cognitive deficits increases with aging in both sexes, but sex differences remain present or become even more prominent al older ages.

There is still much to be learned regarding the specific molecular and cellular pathogenic mechanisms that determine sex-specific characteristics in nervous system diseases and in the deterioration of the nervous system with aging. The exploration of these mechanisms should include not only the analysis of neurons, but also of glial cells, which play an essential role in the protective response activated in the nervous system in an attempt to recover tissue homeostasis after injury and for this reason have been the focus of the present review.

Here we have discussed the role of glial cells in the generation of sex differences in the adaption of the nervous system to pathological conditions. From this analysis we can conclude that glial cells react to pathology with sex-specific characteristics. Indeed, male and female astrocytes differ in their secretion of trophic factors, neuroinflammatory molecules and neuroactive steroids, in their metabolic supply to neurons and in their control of the neurovascular unit and the blood brain barrier. Male and female microglia differ in their migratory, phagocytic and immune response and, together with astrocytes, in the formation of glial scars. Oligodendrocyte progenitors show sex differences in proliferation and differentiation, while oligodendrocytes in the CNS and Schwann cells in the PNS show sex differences in the expression of myelin proteins and in their remyelination activity (Fig. 1).

Although we must assume that the primary reaction of glial cells to tissue injury has evolved to reestablish homeostatic conditions in both sexes, we have seen in the previous sections that the divergent response of male and female glia under pathological conditions results in differences in their neuroprotective and regenerative effects. Therefore, it is important to explore the causes for these differences in glial reactivity to injury. We have discussed here three possible causes: sex chromosome genes, gonadal hormones and neuroactive steroids.

A source of differences in glia is the sex chromosome complement, which not only determines gonadal differentiation, and therefore the levels of gonadal hormones and of their neuroactive metabolites, but also exerts direct transcriptional actions on glial cells. Indeed, genes of the X chromosome expressed by glia are a common cause of the pathological alterations detected in X-linked diseases and the experimental evidence reviewed here suggests that sex chromosome genes also determine the response of glial cells to many other pathological alterations of the nervous system.

Gonadal hormones probably also contribute to the generation of sex differences in the response of glial cells to diseases of the nervous system. Indeed, as we have discussed in the previous sections, glial cells express receptors for gonadal hormones and are therefore a direct target of their actions in the nervous system. Glial cells, in addition, metabolize gonadal hormones into steroid neuroactive molecules, which in turn activate neuroprotective responses in other glial cells and neurons. Therefore, the divergent protective and reparative mechanisms activated in male and female glial cells in reaction to pathological insults are probably determined by a combination of effects by sex chromosome genes, gonadal hormones and neuroactive steroids (Fig. 2).

In summary, the studies discussed in this review suggest that glial cells play a major role in the generation of sex differences in the pathological alterations of the nervous system. Glial cells may therefore represent a relevant target for sex-specific therapeutic interventions for nervous system diseases and aging-associated brain deterioration.

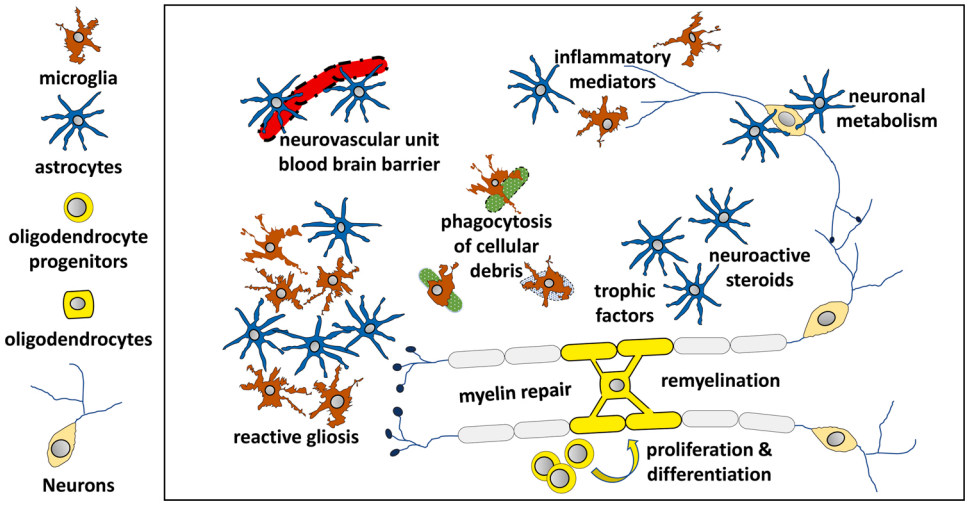

Fig. 1. In the injured CNS, oligodendrocyte progenitors, oligodendrocytes, astrocytes and microglia contribute to the generation of sex-specific neuroprotective and neuroregenerative responses. Male and female astrocytes differ in their secretion of neurotrophic factors, neuroinflammatory molecules and neuroactive steroids and in their metabolic supply to neurons. Male and female microglia differ in their migratory, phagocytic and immune responses and in their formation of glial scars with astrocytes. Oligodendrocyte progenitors show sex differences in proliferation and differentiation, while oligodendrocytes in the CNS and Schwann cells in the PNS show sex differences in the expression of myelin proteins and in their remyelination activity. These different responses of male and female glial cells contribute to generate sex-specific adjustments in neuronal survival, in axonal and white matter regeneration, in the function of the neurovascular unit and in the integrity of the blood brain barrier.

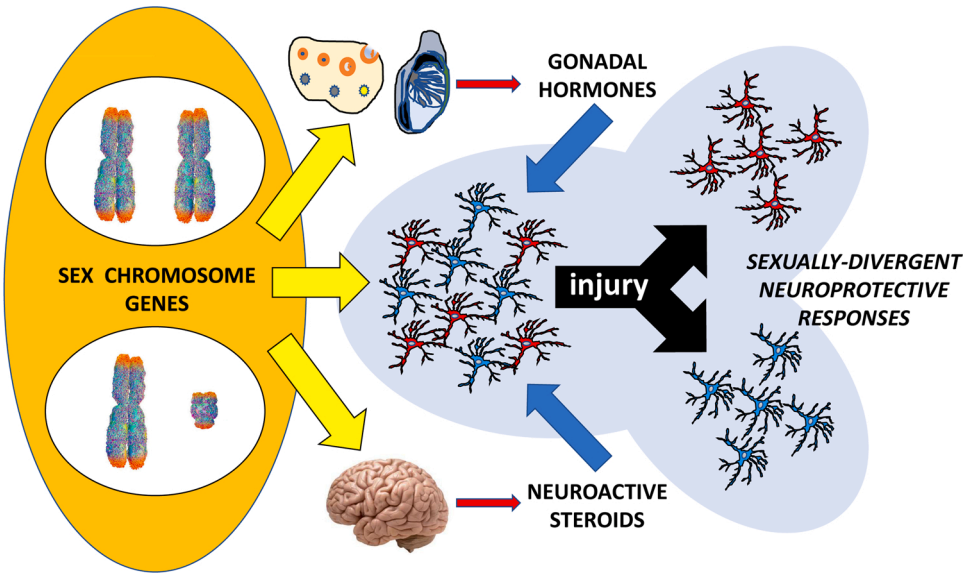

Fig. 2. Sex chromosome genes determine hormonal-dependent and hormonal-independent sex differences in glial cells. In addition, sex chromosome genes interact with gonadal hormones and neuroactive steroids to elicit sex-specific neuroprotective and neuroreparative responses in glial cells after nervous system injury.

Declaration of Competing Interest

The authors report no declarations of interest.

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