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Sexual Steroids and their Receptors Affect Microglia-Mediated Neuroinflammation in Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases have been marked by neuroinflammation and remarkable sexual differences in prevalence and pathology preclinically and clinically. Microglia, the resident innate immune cells in the brain, present sexual dimorphism in terms of number, morphology, and distribution in neurodegenerative diseases, especially in Alzheimer's disease and Parkinson's disease. This sexual dimorphism of microglia play as a big fish in healthy and disorder brain. But the mechanisms for the divergence are not well known. Microglia plays an active role in early healthy male and female brain development, including sexual differentiation and development of neurodegenerative diseases. It has been found that microglia are a key fastener involved in neurodegenerative diseases and sexual steroids, such as estrogen, testosterone, and progesterone, have anti-inflammatory effects on microglia-mediated neuroinflammation. The interaction between sexual hormone and neuroinflammation in male and female's neuroimmune signal catches researchers' eyes at a high rate of speed. Here we focus on recent advances in microglia-mediated neuroinflammation relative with gender differences in neurodegenerative diseases.**Keywords:** IgA vasculitis; Henoch-Schönlein Purpura; Abdominal Phenotype; Gastrointestinal Endoscopy

Abbreviations: AD: Alzheimer's Disease; PD: Parkinson's Disease; POA: Preoptic Area; LPS: Lipopolysaccharide; MCI: Mild Cognitive in Impairment; FTD: Frontotemporal Dementia; PGE2: Prostaglandin E2; ERs: Estrogen Receptors; MS: Multiple Sclerosis; ERE: Estrogen Response Element; P3: Postnatal Day 3; EAE: Experimental Autoimmune Encephalomyelitis; TLR4: Toll-Like Receptor 4; RAS: Renin Angiotensin System; TREM2: Triggering Receptor Expressed on Myeloid Cells; PYD: Pyrin Domain; AIM2: Absent in Melanoma2; ROS: Reactive Oxygen Species; iNOS: inducible Nitricoxide Synthase; Nrf: Nuclear Factor; PPAR-γ: Peroxisome Proliferator-Activated Receptor-γ; PR: Progesterone Receptor; AR: Androgen Receptor

Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), are generally featured by neuroinflammation and procedural loss of selectively vulnerable populations of neurons, which lead to cognitive impairment, dementia and decline in motor functions [1,2]. The most common pathologies of neurodegenerative diseases are amyloidosis, tauopathies, α-synucleinopathies, and transactivation response DNA binding protein 43 (TPD-43) [1]. Moreover, amyloidosis, tauopathies, and α-synucleinopathies are all associated with neuroinflammation and microglial activation [3-5]. Through phagocytosing abnormal synaptic constituents of neurons, microglia play active roles in synaptic disorders. Moreover, microglia are also associated with synaptic spreading of tau, which is related to the activation of NLRP3 inflammasome [6]. Early microglia responses predicted an improved cognition in PS2APP amyloid mouse model, which suggested the innate immune system could constitute a more relevant therapeutic target [7]. The prevalent of

neurodegenerative diseases is increasing, and abundant preclinical and clinical data demonstrate that neurodegenerative diseases disproportionately affect male and female in both prevalence and symptom progression [8,9].

Surprisingly, sexual difference existed in microglia isolated from animals. Moreover, microglia in mice emerged sex divergences in different age, especially in older mice. These studies suggested that microglial gender differences could tend to emerge more eminently in aging and age-related disorders, such as neurodegenerative diseases [10]. Sex differences in neurodegenerative diseases are finally attributed to sexual chromosome and sexual hormone. Such as SRY, a Y-chromosome gene, directly contributes to the gender differences in the 6-OHDA-induced rat model of PD [11]. Furthermore, estrogen act on microglia by attenuating the response to inflammatory stimulation and regulating microglial proliferation [12]. Women are more twice than men to suffer from AD over 65 years old and cognitive decline is more severe in women. On the contrary, PD is more common in men (1:3.5) [13]. In an animal experiment, females have more microglia in several specific brain regions than males in healthy adult rats [14], which may account for gender differences in susceptibility to CNS diseases. Microglia, the resident innate immune cells in the brain, has been long well-documented to be decisive for maintaining the homeostasis of the CNS.

It was reported that the sexual differences of susceptibility to neurodegenerative disorders maybe start with genes [8]. In recent years, sex specificity of microglia has become a hot topic in studies because its immune functions are associated with sexual differentiation in neurodegenerative diseases. Gonadal hormones are paramount importance for microglial sex differences. Modulated by sex hormones, the roles and mechanisms of microglia are different in the process of associated neuroinflammation. Both estrogens and androgens play significantly neuroprotective roles in the adult brain and attenuate multiple aspects of AD- and PD-associated neuropathology [9,15]. In addition, the X chromosome, containing a mass of immune-associated genes, is another connection between immunity and gender. In the developing of female preoptic area (POA), immune-related genes are enriched significantly after the suppression of DNA methyltransferase activity [16]. Therefore, the X chromosome may influence the immune response in a number of ways, leading to sexual differentiation.

Sexual Dimorphism of Microglia in Healthy and Disorder Brain

Microglia account for 5 to 15% of adult no-neuronal cells that varies in distinct brain regions and make up a large number of immune cells of brain. Under physiological conditions, microglia hold uniqueness in location within the brain parenchyma, and they can directly contact with neuron, neural progenitors and other cells in these parenchymas [17]. Microglia act as the central junction between inflammation and neurodegenerative disease [13]. The cell has two major functions: watching over the overall health of neurons and synapses and examining the brain for potential threats and problems. When microglia detect abnormal substances, such as amyloid or damaged cell debris, they become activated and signal to other microglia to execute clean-up tasks orderly [17,18]. There are sexual dimorphism of brain regions, including POA of hypothalamus, spinal nucleus of the bulbocavernosus, and developing hippocampus, amygdala, and cortex [19]. Meanwhile, neurons, astrocytes and microglia exhibit gender specificity in cell number, distribution and function [20]. Especially astrocytes, another important immune cells in the brain. However, in the last 10 years, microglia have received more attention about gender than astrocytes (Figure 1).

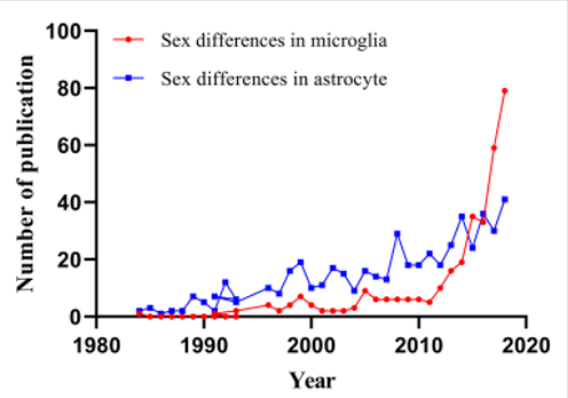

Figure 1: Comparison of publications on microglia and astrocytes in relation to sex in the title or in the abstract.

Human transcriptomes of the brain at different age and the brain span dataset illustrated that gene associated with microglia phagocytic and immune function are highly expressed [21]. The sex-dependent pro-inflammatory profile could be a microglia-specific feature, which is lacking in function-similar macrophages [22]. All of these increasingly affirm these indispensable roles of microglia in sexual dimorphism of the brain (Figure 1). During the process of microglia maturation, sexual dimorphism of microglia has an earlier impact on male than female. Moreover, there is an obvious acceleration in male microglial development after treated with lipopolysaccharide (LPS), while female microglia have no changes during their maturation stages. These documents suggested that male microglia would be more susceptive to neuroinflammative agents, which could answer for rapid aging of microglia and brain dysfunction [23]. Namely, although differences are limited in their colonization patterns, male and female primary microglia have shown several gender-specific divergences in their transcriptomic signatures. Female primary microglia presented higher expression levels of genes related to inflammation, apoptosis, and LPS response [24].

Moreover, through abundant detections of major histocompatibility complex molecules (MHC) from microglia isolated from cortex and hippocampus, higher antigen-presenting capacity of microglia was discovered in naive males [25]. There are more than 500 divergently expressed genes between males and females [22]. A report about molecular signature analysis

of transcription factors suggested NF-κB, a transcription factor associated with the regulation of genes, more expressed in males than females. Microglia isolated from female mice showed a neuroprotective phenotype independent of hormonal cues, which was retained when these neuroprotective microglia were transferred into brains of male mice [22]. Analogously, subsequent studies revealed transcriptomic features of male microglia towards pro-inflammatory functions and luciferase activities were 2.4-time higher than female microglia [25]. There are numeral and morphological variances in different brain regions of female and male rodents [26]. Amygdala, POA, hippocampus and cortex are the main brain regions in which microglial sex differences [27-30]. In the developing POA, there are more ameboid-shaped microglia in male brains, while female brains possess more surveying microglia, which suggests that the interaction between microglia and gonadal hormones play a crucial role in the development of the POA [28,31].

Sex Dimorphism in Prevalence and Development of Dementia

AD is the most common one of neurodegenerative diseases, with more than 35.6 million persons worldwide estimated to be affected. The number of Alzheimer's patients is expected to almost double every 20 years and will add to 65.7 million in 2030 and to 115.4 million in 2050 [32]. A recent estimate suggested that the global costs for dementia will be 9.12 trillion in 2050, which is more 4.8 folds than the prediction made by the world Alzheimer Report 2015 [33]. One clinical-pathologic study reported that the incidence of AD is higher in women, exactly 1.33 times than in men aged over 70 years old. This higher incidence in women was observed more previously from 60-64 years old to 95 years old [34,35]. A review discussed key differences between male and female patients with AD as follows: firstly, men and women undergoing AD present diverse cognitive and psychiatric symptoms, and females present rapider cognitive decline after diagnosed with mild cognitive in impairment (MCI) or dementia.

Secondly, women have more neuronal tangles in both mesial temporal and neocortical areas. Thirdly, the rate and pattern of brain atrophy vary among AD patients of different genders, women had more AD pathologic diagnosis, especially had more tau tangles density. MCI found that atrophy of brain is rapider in females than in males [36]. The gender difference in AD incidence may be related to age [37]. However, no interaction was found between gender and age, and no linear association between age and AD pathologies, which similarly attested that women have a higher incidence of AD than men, regardless of age [38]. Frontotemporal dementia (FTD) is one of the major progressive neurodegenerative diseases. Similar to other types of dementia, much evidence suggests that neuroinflammation is a major factor of the pathogenic process, involving excessive microglial activation, astrocytosis, cortical inflammation, and divergent expression of inflammatory cytokines in the periphery [39]. A meta-analysis referring to sex differences in FTD revealed the same outcome as other dementias-a higher prevalence of female patients with GRN-relative FTD than male patients [40].

Under basal conditions and in the presence of proinflammatory stimuli, male microglia showed a markedly increased migratory capacity compared with female microglia *in vitro*. Oppositely, female microglia exhibited significant enhanced basal and stimulated phagocytic activity [41]. Anti-aging drugs, such as acarbose, 17-a-estradiol and nordihydroguaiaretic acid, reduced the number of microglia, as well as age-associated overproduction of TNF-a in the hypothalamus of male UM-HET3 mice, but these effects are not founded in female mice, which suggests that microglial activation in the hypothalamiccould is effected by drug-induced changes in a gender-specific manner [42]. That sex-dimorphism preference in neurodegeneration might be meditated by estrogen-induced kallikrein-8 (KLK8) overproduction which emerged in neuronal and microglial cells long before AD pathology [43].

Mechanisms: The Role of Estrogen and Testosterone in Microglia Actions and Neuroinflammation

The CNS is a principally steroidogenic environment to synthesize and metabolize steroids stemming from the circulation. Microglial neuroinflammation can severely affect neurosteroid synthesis, vice versa, steroids can in return mediate microglial neuroinflammation, such as 17β-E2, testosterone and allopregnanolone [44]. During the development of hippocampus and cortex, the expression of the C-C motif chemokine ligands 20(CCL20) and C-C motif chemokine ligands 4(CCL4) in the developing male hippocampus and cortex are more than 200-fold and 50-fold compared with those of female respectively, which results in the divergent perinatal colonization of brain areas concerned with cognition and memory and plays a role in highly gender divergent hippocampus, amygdala, and cortex. The result suggests that much more sex hormones involved in the development of male brain [14,45]. Nowadays, plenty of researches have shown that sexual differentiation and microglia during the brain development play critical roles in neuroinflammation. Microglia increased estradiol production and promoted neuronalsecretion of prostaglandin E2 (PGE2) [19]. Several documents suggested that other inflammatory agents may participate in sex divergence in brains, particularly during the developmental processes.

Meanwhile, studies have also found significant gender divergences in the expression of several inflammatory genes and pro-inflammatory cytokines in the developing POA. *In vitro*, male and female microglia have shown different inflammatory signaling to LPS and estradiol treatment [46], which argues that in gender differences of brain, microglia may be not only in number or morphology, but may also be phenotypic. Gender differences were appeared in normal neurodevelopment of rodents during several stages, which could affect the dynamically interactions between glia and neurons. Therefore, these stages would be set for both resistance and sensibility to the deterioration of the neurodegenerative diseases in a gender-specific manner [23]. Steroid hormone

receptors are differently expressed in different sources of microglia, including BV2 and primary microglia isolated from adult mouse brains [47]. Moreover, these receptors are differently distributed in microglia by quantitative and morphological in normal and injured brains. Both estrogens and testosterones exert anti-inflammatory effects on microglia [48].

Estrogen

Classical Estrogen Receptors and Functions (ER): Estrogens, produced mainly by the ovary, are highly involved in the development of femaleness and maternal functions. Meanwhile, estrogens exert several effects on a large proportion of organs, including brains. Estrogens can go through the BBB and be endogenously produced by the brain relying on its own cholesterol [49]. Estrogens are exposed in females including estrone (E1), estradiol (17-β-estradiol, E2) and estriol (E3), and E2 is the primary and most effective circulating estrogen. Estrogens and estrogen receptors (ERs) are identified as anti-inflammatory factors in the model of Multiple Sclerosis (MS), which suggested that estrogens and ERs may take part in physiological regulation of neuroinflammation [50]. Functions of estrogens and ERs in brains are extremely complex. ERs possess two classical subtypes: ER type 1(ER1; mainly named as ERα) and ER type 2 (ER2; mainly named as ERβ). Both of them can bind to 17β-E2 and activate estrogen-regulated genes [51,52]. The third ER called G-Protein–Coupled ER (GPER1, commonly named as GPR30) is a membrane ER in several tissues [53,54]. Additionally, several splice variants have been demonstrated, which may be the reason for divergences to estrogens. ERs translocate to the nucleus and bind directly to specific estrogen response element (ERE) sequences on the DNA or to other transcriptional factors to regulate genic expression [49,55,56].

Membrane-bound ERα and ERβ are also involved in activation of fast-acting signaling pathways. GPR30 could traverse the plasma membrane and trigger rapid signaling cascades [54,57]. Orderly activation of ERs may lead to initially rapid responses followed by genic expression and will regulate the long-term responses [58]. They differ considerably in different cell systems with different structure and function and bind to different estrogenic isomers. The expression of sex steroids receptors on microglia is associated with the phase of brain maturation and microglia are more sensitive to estrogens with older age: the level of ERα mRNA is detectable in microglia purified from mice at postnatal day 3 (P3) and up-regulates in adult mice [59]. The expression of ERβ from primary microglia can be detected in from P0 newborns but is undetectable starting from P3 until adulthood [47,60]. ERs knock-out mice models have certified that the specific activation of the ERα in the brain is responsible to mediate the neuroprotective effects of estrogens [61]. ERβ, expressed in $CD11c^+$ microglia exerts indispensible effects in operating neuroprotection. Once ERβ was specifically removed from $CD11c^+$ microglia during experimental autoimmune encephalomyelitis (EAE), the neuroprotection of ERβ-ligand treatment was lost [62].

Non-Classical Estrogen Receptors and Functions (GPR30): The GPR30, a receptor binding 17β-E2 with high affinity, is recognized to play necessary roles in brain dysfunction. Mechanisms of specific activation to the GPR30 by 17β-E2 has been demonstrated [63]. GPR30 distributes extensively and covers almost all brain regions [64]. Through using polyclonal antibodies to defense against the human C-terminus of GPR30, researchers revealed an analogous spatial pattern in brains of rats [64], mice [65] and humans [66,67]. The immunoreactivity and mRNA expression of GPR30 were remarkable in forebrain of rats, such as hippocampi, frontal cortexes, medial septumes, diagonal band of brocas, nucleus basalis magnocellularises and the striatumes [63,68].

Specific ERs of Microglia in Anti-Neuroinflammatory Responses: Lots of evidences testify the importance of estrogens in neurodegenerative diseases. Nevertheless, there is an uninterrupted controversy concerning whether ERs or GPR 30 takes the beneficial effects on microglia. On the one hand, early studies indicated that ERα is a primary target for estradiol to produce anti-inflammatory effects in the brain [69]. Transcription factors can activate ERα acting as a ligand, but this activation is ligand independent. So far, little is known about neuroinflammatory signaling of microglia mediated by ERα in neurodegeneration. An experiment demonstrated that ERα expressed in neuron takes part in the neuropretective effects of estrogen [70]. In addition, ERα mediated immune response and microglial activation, which happened in the brains of women who are estrogen deficient or estrogen aging [71].

On the other hand, it is not ERα but ERβ predominately expressed in microglia .What's more, ERβ-selective agonists could ameliorate some experimental immune diseases by means of regulation to T cells and microglia [72]. Moreover, 5-androsten-3β and 17β-E2 synthesized by microglia showed that reduction of ADIOL or ERβ expression resulted in exaggerated inflammatory responses to toll-like receptor 4 (TLR4) agonists. And the murine BV2 microglia cell line selectively expresses ERβ. These results provided evidence that an ADIOL/ERβ/CtBP-transrepression pathway mediates inflammatory responses in microglia and can be selectively targeted by ERβ modulators by controlling the inflammatiory magnitude and duration in microglia and astrocytes [73,74]. GPR-30 was also detected in primary microglia purified from rat brains. Moreover, researchers have revealed that GPR-30 agonist could obviously inhibit the accumulation of microglia [75].

Effects of Estrogen on Microglial Activation: The changes of sex steroid, such as estrogen in females and testosterone in males, are associated with an increasing risk of neurodegenerative diseases [58]. The postmenopausal women have a significantly decreasing risk of AD by applying hormone replacement therapy

(HRT), accompanied by the decline in number of phagocytic microglia [76]. Furthermore, ovariectomy(OVX) decrease ERα level that deteriorate brain damage, and exacerbatepost-stroke inflammation. To be more specific, OVX can enhance angiotensin and NADPH-oxidase activity, as well as increase the expression of neuroinflammatory markers. But these effects are changed by estrogens. During that process ERα and the brain renin-angiotensin system play a major role [77]. Estrogens exert anti-inflammatory and neuroprotective effects in the central nervous system. Studies revealed that microglia can express subsets of classical, non-classical ERs and progesterone receptors in a dynamic way [78]. Microglia are involved in ERα-induced regulation of local renin angiotensin system (RAS) [58,77]. These facts could indicate that estrogens generally enhance the immune system.

Therefore, among sex steroids, estrogens have been received the most attention in preclinical and clinical investigation [79]. Microglia has no ERα in the POA, an important brain area for sexual behavior, and is featured by prominent neuroanatomical gender differences [27]. Exogenous estrogens have immune-enhancing effects on humoral immunity and may mediate cell-mediated immunity at different dose. However, exogenous testosterone can simultaneously depress both humoral and cell-mediated immunity and increase sensibility to bacterial and viral infections [80]. When activated primary microglia were treated with 17β-estradiol, inducible nitricoxide synthase (iNOS) and reactive oxygen species (ROS) were declined [75,81,82]. It has been shown that estrogens could produce anti-oxidant and anti-inflammatory effects by activating endogenous inflammatory signaling, such as phosphatidylinositol 3-kinase /protein kinase B (PI3K) [83] /nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and peroxisome proliferator-activated receptor-γ(PPAR-γ) [84,85]. Furthermore, a wealth of experimental models indicated that deficit in endogenous estrogens facilitates the onset of inflammation, and these inflammation reactions could be antagonized by estrogen replacement.

In many inflammatory models, estrogens clearly opposes the inflammatory process by blocking the synthesis of proinflammatory mediators, hematopoietic growth factors and cell differentiation agents [61]. Estrogens can decrease the production of inflammatory cytokines through intervening TLR signaling pathways associated with AP-1and NF-κB. Evidences showed that NF-κB p65 is damaged by estrogens through a non-genomic pathway. ERα can inhibit NF-κB activity by the induction of IκBα, an inhibiter of NF-κB. Equally, AP-1 is associated with effects of estrogens, for which the p85 PI3K signaling pathway is related to estrogen-dependent blocking of TLR4 signal pathway [47] (Figure 2). In the presence of inflammatory responses, estrogen regulates cytokine expression at basal levels through microglia [86], while testosterone and androgen have an inhibitory effect on glial activation [87].

However, how these sex steroids specially alter the microglial activity leading to gender divergence of the brain is still not understood [79,80]. Testosterone is converted to 17β-E2 by aromatization in neurons, and after that process, testosterone can exert its reproductive capacity via ERs. Both male and female brains of fetus are exposed environment with high levels of estrogens produced by placentas and mothers. Nevertheless, in female fetus, α-fetoproteins bind estrogen and act as carriers, which protects fetal brains from virilising effects of estrogens by stopping estrogens to entry into cells [88,89]. Surprisingly, fetal and postnatal microglia are strongly associated with this process through mediating the release of sex steroids especially in the POA, which results in microglial activation and affects fetal brain programming in a gender-dimorph manner [19].

Testosterone and Progesterone: A study found progesterone has therapeutic effects on microglia activation and neuroinflammation. Progesterone therapy deceased neurological behavioral deficits. In addition, progesterone therapy reduces the mRNA expression levels of M1-markers in corpus callosum regions, while the expression of M2-markers was significantly increased, such as triggering receptor expressed on myeloid cells (TREM2) , CD206, Arg-1 and TGF-β. Furthermore, progesterone therapy significantly decreases the mRNA and protein expression levels of NACHT-, LRP- and pyrin (PYD)-domain-containing protein 3 (NLRP3) and IL-18 (~2 fold) [90], and it is plausible that progesterone could act on other inflammasomes regulation at the microglial level, such as NACHT-,LRP- and pyrin (PYD)-domain-containing protein 1 (NLRP1), absent in melanoma2 (AIM2)and NOD-like receptor family apoptosis inhibitory protein (NAIP-NLRC4).

Data showed that supplementation of testosterones in castrated male mice restored tight junction integrity, the BBB selective permeability and the inflammatory features was almost abolished, such as iNOS, cyclooxygenase 2 (COX-2), interleukin 1 beta (IL-1β) and TNF-α [91-98]. During embryogenesis in humans and neonatally in rodents, production of testosterone is responsible for the masculinization of selected brain circuits which control sexually divergent behaviors and physiological processes. In line with these evidences, microglial gender divergences in number and morphology appear not until testosterones soar at P4 when more morphology-activated microglia in male rats. That pattern was shifted until P [30], which is previous to the onset of adult circulating hormones [14]. Although progesterone receptor (PR) and androgen receptor (AR) are not discovered in adult microglia, data show that developing microglia express both PR and AR, which results in microglia respond to the surge in testosterone and adjust microglia into a male-specific pattern of maturation [59] (Tables 1-3)(Figure 2).

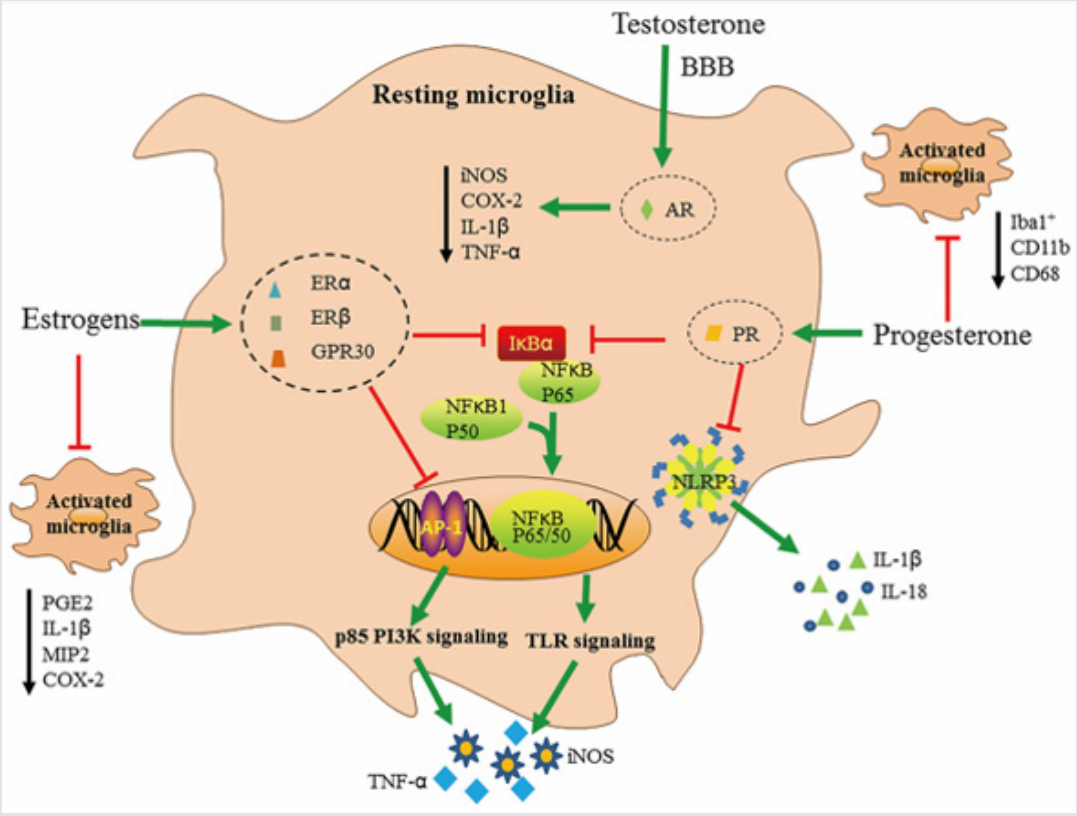

Figure 2: The anti-inflammatory effects of estrogens, testosterone and progesterone on microglia, Firstly, estrogens take anti-inflammatory effects by combining with their receptors (ERα, ERβ and GPR30). They inhibit the production of in cytokines by interfering with TLR signaling through NF-κB and AP- I. ERα inhibits NF-κB activity by inducing the synthesis of its inhibitory protein-IkBα. Similarly, AP-1 is involved in the actions of estrogen by p85 PI3K signaling. Estrogens also inhibit the activation of microglia. Secondly, progesterone and its receptor PR could inhibit NF-κB and NLRP3 inflammasome activity resulting in lower reduction of IL-1β, IL-18, COX-2, and PGE2, Lastly, testosterone holds the BBB selective permeability, tight junction integrity and almost completely abrogated the inflammatory features, such as iNOS, COX-2, lL-lβ and TNF-α.

Table 1: Neuroinflammation presents sexual dimorphism in different models of Alzheimer's disease.

Model	Exposure	Effects	Reference
AD patients		Female AD patients had higher levels of CHI3L in cerebellums than males.	[92]
Tg CRND mice	2 months old of postnatal age (P60)	Neuroinflammation was more prominent in females at later disease stages.	[43]
C57BL6 mice	3, 12 and 24 months old	Inflammatory genes were enhanced in females compared with age-matched males, and aging-associated genes highly spread for microglia-specific transcripts.	[93]
Tg 2576 mice	6 and 14 months old	Oligomeric and monomeric Aβ were decreased in female hippocampi but increased in males when mt1 was overexpression.	[94]
APP/PS1 mice	16 months old	TSPO was significantly higher in female mice.	[95]
LPS-induced APP/PS1 mice	4.5-month-old mice were treated with 100μg/kg LPS	Female hippocampi were more tolerant to acute inflammation.	[96]
APP/PS1/tau triple-transgenic mice	12 months old	Female mice displayed more prominent neuroinflammation than male 3x Tg mice.	[97]
Primary male and female microglia	From forebrains of wistar rat's newborn to 2 days, and stimulated by 20ng/mL TFN-γ for 24 hours	Male microglia showed higher migration, but female microglia showed higher basal and stimulated phagocytic activity.	[41]

Abbreviations: CHI3L: Chitinase-3-Like 1 Protein; Aβ: Amyloid-β; TSPO: Translocator Protein of 18 kDa; LPS: lipopolysaccharide; TFN-γ: Interferon-g; MT-1: Metallothionein-1.

Table 2: Effects of estrogens and progestogens on neuroinflammation in different models of Alzheimer's disease.

Sex Hormone	Model	Exposure	Effects	Reference
Estrogens	APP23 mice	Ovariectomy	Pathological signs of AD and microglial activation were increased.	[98]
	ICR rats	Ovariectomied when 9 months old	Microgliosis and astrogliosis and NF-κB activation were increased.	
	SD rats	OVX, 10-15 pg/mL 17β-estradiol in mini-pumps (0.5 μL/hour, 14-day release)	NLRP3 inflammasome formation was negatively regulated.	
	BV2 cells	$A\beta_{1-42}$ (1μM) and β-estradiol (10 μM) for 24 hours	Microglial inflammatory responses were decreased.	
	BV2 cells	Hypoxic stimulation for 3 hours and treated with 17β-estradiol (27.24 ng/mL)	NLRP3 inflammasome formation was negatively regulated.	
Progestogens	SD rats	$A\beta_{25-35}$ (2 g/L) injected into the bilateral hippocampus CA1 region and treated with progestogens (4 mg/kg, 8 mg/kg and 16 mg/kg)	expressions of TNF and IL-1β were decreased in a dose-dependent manner.	
	3xTg mice	allopregnanolone (10 mg/kg) respectively for 1/month 1/week/6 months, and 3/week/3 months regimens single injection	Administration of allopregnanolone decreased microglial activation.	
	BV2 cells	Hypoxic stimulation for 3 hours and treated with progestogens (31.45 ng/mL)	Inflammasome activation in microglia was dampened.	

Table 3: Effects of estrogens and progestogens on neuroinflammation in different models of Parkinson disease.

Sex Hormone	Model	Exposure	Effects	Reference
Estrogens	AD patients	Recruited from the Swedish population	ERβ genes polymorphismcorrelate with early age disease onset.	[98]
	human		Women suffering unilateral or bilateral ovariectomy before the onset of menopause showed higher risks of PD.	
	wistar rats	OVX	Microglial activation is increased, while expression of microglia-mediated genes is downregulated .	
	C57BL/6N mice	Ovariectomized when 10 weeks old and were given17β-E 0.01mg/day	6-OHDA and MPTP –induced ovariectomized mice present heavier neuronal damage and stronger microgliosis compared.	
	C57BL mice	female mice was induced by MPTP	Male mice presented faster iNOS and more dopamine after MPTP treatment compared to females.	
	C57BL/6 mice; BV2 cells	MPTP-induced mice were given 5μg G1and 10 μg G15 twice/day for 12 days; 100 μM MPP was treated to BV2 with G1 (1, 10, and 100 nM) or G15 (100 nM) for 24h	G1 inhabited microglial activation and increased dopaminergic neuronal cell survival in male MPTP-treated mice.	
	WT, ERαKO, and ERβKO female mice	Ovariectomized when 10–15weeks, 7 days after OVX, all mice received injection of LPS(5mg/kg) and treated with 180 μg/mL E2	17β-E2 reduced proinflammatory cytokines (IL-1, TNF, IL-6, IL-12 p40) and the chemokine rantes in the female brains.	
	Primary microglia from 1-2-day-old Wistar rats; and SH-SY5Y cell	Microglia were pretreated with Tam or Rlx and then treated with 10 ng/mL LPS for 6 h; SH-SY5Y were pretreated with Tam or Rlx for 24 h and then treated with 10 ng/mL LPS for 24 h.	SERMs can suppress production of proinflammatory cytokines and chemokines, such as TNF-α, IL-1β, MCP1 or MIP2 in microglia	
Progestogens	BV-2	BV2 were pretreated with progesterone for 1h, then treated with 10 ng/mL LPS for 4h.	NF-κB and JNK pathways, as well as TNF and iNOS production were inhabited by progesterone.	

Abbreviations: OVX: Ovariectomized; MPTP: 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; SERMs: Selective Estrogen Receptor Modulators; MCP1: Monocyte Chemotactic Protein-1; MIP2: Macrophage Inflammationprotein-2; GFAP : Glial Fibrillary Acidic Protein

Directions

Since neurodegenerative diseases were first described more than 100 years ago, almost all of focuses were laid on the gross anatomical changes, such as excessive tau phosphorylation, superabundant protein aggregation and outnumbered neuron loss. Nevertheless, more and more mechanistic, genetic, and histopathological documents point to inflammation-related changes such inflammatory cytokines, immune cell proliferation and migration of inflammatory cells, highly dynamic phagocytosis, and reactive gliosis as general characteristics of neurodegenerative diseases, such as TREM2, inflammasomes and inflammatory complement cascades [99-101], which were long recognized as secondary or reactive responses to latent processes. Meanwhile, recently emerging evidences also start to break through the stereotypes and identify the immune system as the central player in disease occurrence and deterioration, and new functional aspects of these inflammatory signaling pathways are highlighted [102]. For example, Nlrp3 knock-out APP/PS1 transgenic mice presented fewer inflammatory cytokines and phosphorylated tau protein, as well as amyloid deposits.

A risk genes analysis about PD pathway founds prominent pregnancy in several adaptive immune cells and immune signaling pathways. Pathogenic types of α-synuclein could induce immune responses in T cells which were purified from Parkinson's patients [103,104]. Sex differences in neurodegenerative diseases mainly exist in microglia, which play indispensible role in neuroinflammation. Nowadays, neuroinflammation is becoming the focus of neurodegeneration. Surprisingly, Aβ might be a neuroprotective hero in the onset of neurodegenerative diseases, and infectious or sterile inflammatory stimulus might impulse amyloidsis [105]. Glial cells exert as important participants to the development and homeostasis of the central nervous system. Especially, microglia play the major role as the crossroad binding the immune reaction and the nervous system, each of which is extremely critical for the owner to percept external and internal environments16. In conclusion, it may be a promising research direction to explore the neuroinflammation, immune-mediated mechanisms and the application of immunomodulation. Anti-inflammation in the brain and immune-modification strategy aiming at male and female in the way of precision medicine would be renewing and spark cure to neurodegenerative disorders.

Consent for Publication

Not applicable.

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None.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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