Published in final edited form as:
Front Neuroendocrinol. 2008 October ; 29(4): 507–519. doi:10.1016/j.yfrne.2008.04.001.

Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases

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Abstract

Recent studies highlight the prominent role played by estrogens in protecting the central nervous system (CNS) against the noxious consequences of a chronic inflammatory reaction. The neurodegenerative process of several CNS diseases, including Multiple Sclerosis, Alzheimer's and Parkinson's Diseases, is associated with the activation of microglia cells, which drive the resident inflammatory response. Chronically stimulated during neurodegeneration, microglia cells are thought to provide detrimental effects on surrounding neurons. The inhibitory activity of estrogens on neuroinflammation and specifically on microglia might thus be considered as a beneficial therapeutic opportunity for delaying the onset or progression of neurodegenerative diseases; in addition, understanding the peculiar activity of this female hormone on inflammatory signalling pathways will possibly lead to the development of selected anti-inflammatory molecules. This review summarises the evidence for the involvement of microglia in neuroinflammation and the anti-inflammatory activity played by estrogens specifically in microglia.

Keywords

Estrogen; microglia; neuroinflammation; Multiple Sclerosis; Alzheimer's disease; Parkinson's disease

1. Introduction

Substantial evidence supports the role of neuroinflammation in the pathogenesis and progression of neurodegenerative diseases; microglia cells are the resident inflammatory cells of the brain that are primarily involved in promoting brain inflammation in response to both acute or chronic stimuli. Improving our understanding of microglia cells regulation represents a major advancement for future strategies aimed at controlling pathologies, such as multiple Sclerosis (MS), Alzheimer's disease (AD) and Parkinson's disease (PD), that are associated with a relevant neuroinflammatory process. The estrogen hormone has a well-known neuroprotective activity, which could be related with the gender prevalence of selected neurodegenerative diseases. Accordingly, the strong effects on the incidence and symptomatology of certain neurodegenerative pathologies observed during pregnancy or at menopause or triggered by the administration of estrogenic drugs have been ascribed to estrogen action in brain cells. Given that a large body of evidence now indicates that estrogens

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exert an anti-inflammatory activity, we propose that part of its neuroprotective effects may be linked to the inhibition of microglia activation. The aim of the present review is to provide the state-of-the-art knowledge on estrogen action in microglia in selected disorders, such as MS, AD and PD, and to support the hypothesis that the use of estrogens in preventive therapies might delay the onset of neurodegeneration.

2. Inflammation and neurodegeneration

Role of microglia in neurodegeneration

Over the past two decades evidence accumulated from both experimental and post-mortem studies suggested that a sustained inflammatory reaction is present in chronic neurodegenerative states. In addition, a number of proinflammatory mediators, such as cytokines, and inflammatory-associated factors such as cyclooxygenase-2 (COX-2) and inducible-nitric oxide synthase (iNOS) are elevated in the CNS or cerebrospinal fluid of neurodegenerative disease patients. Furthermore, recent epidemiological studies indicate that the chronic use of nonsteroidal anti-inflammatory agents (NSAIDs) reduces the risk of PD and AD ([39], [153], [156] and [227]) and inheritance of polymorphisms resulting in enhanced expression of various inflammatory mediators was reported to increase the risk of these two pathologies ([32] and [248]). Importantly, activated microglia were found at the histopathological sites of several brain disorders, including neurodegenerative diseases such as AD, MS, PD, ALS (amyotrophic lateral sclerosis) and AIDS-associated dementia ([57], [94], [117], [155] and [194]).

Microglia are resident immunocompetent and phagocytic cells of the CNS thought to mediate the innate immune defence and to act as scavenger cells in the event of infection, inflammation, trauma, ischaemia and neurodegeneration in the CNS [129]. Resident microglia in the healthy brain display a “resting state” appearing in a downgraded phenotype, with highly ramified morphology and a low expression of membrane receptors that serve immunological functions [124]; even in this resting state microglia are highly active as shown by the high motility of their processes and protrusions observed by two-photon imaging analysis of brain *in vivo* ([54] and[174]). Microglia are the first cell type that sense any form of disturbance of the brain and rapidly activate through a well-characterized and graded response; the inner cytoskeleton changes and the cell body becomes enlarged, bearing shorter and thicker cytoplasmic processes ([175] and [220]). This activated, macrophage-like appearance associates with phagocytic activity, as activated microglia engulf toxic molecules and cellular debris [14]. In case of a persistent state of activation, as described in several neurodegenerative diseases, the beneficial activity of microglia may however become detrimental and contribute to neuronal dysfunction and progression of the disease.

As a consequence, inflammatory cells and mediators once thought to be involved only in peripheral immune responses are now considered as key factors also in the pathogenesis of neurodegenerative diseases ([148] and [167]). The identification of the mechanisms underlying microglia persistent activation and the key inflammatory mediators involved in neurotoxicity is currently believed to be instrumental to the development of effective inhibitors able to combat neuroinflammation and provide efficacious treatments for neurodegenerative diseases.

Estrogens and microglia

Detecting the expression of the two estrogen receptors (ERs), ERα and ERβ, in cells of the monocyte-macrophage lineage [245] first suggested that estrogens may play a role in inflammatory diseases and several laboratories showed that these hormones act in a variety of macrophage-like cells blunting the inflammatory response triggered by diverse inflammatory stimuli. The last decade witnessed increasing confidence on the anti-inflammatory effect of

estrogens to the point that several Pharmaceutical Companies are presently developing estrogen receptor ligands as anti-inflammatory agents [88]. With regard to microglia, in the recent years our studies showed a major anti-inflammatory activity of estradiol in microglia activated by strong inflammatory stimuli such as lipopolysaccharide (LPS) [244]. This effect was antagonized by ICI182,780, an estrogen receptor antagonist, suggesting a receptor-mediated effect of the hormone and ERα appeared to be selectively involved in estradiol anti-inflammatory activity in brain macrophages ([83] and [242]). Other authors further confirmed these observations using primary cultures of microglia as well as cell lines and assaying estrogen-dependent attenuation of microglia activation in terms of reduced phagocytic activity, production of reactive oxigen and nitrogen species and other factors of the inflammatory cascade ([26], [44], [62], [142] and [264]). Meanwhile, a better evaluation of neurological and neurodegenerative diseases has also pointed to a potential role of estrogens in the pathogenesis and progression of several neuroinflammatory and neurodegenerative diseases, thus providing a new strength to the hypothesis of the potential benefits of the use of estrogenic compounds in the treatment of these disorders. We here review some of the current evidence of the anti-inflammatory role played by estrogens in the manifestation of three major neural diseases: Multiple Sclerosis, Alzheimer's and Parkinson's disease.

3. Neuroinflammation, microglia and neurodegenerative disorders

3.1 Multiple sclerosis and neuroinflammation

Multiple sclerosis (MS) is the most common cause of neurological disability in young adults in the Western world that begins with relapsing/remitting episodes and eventually evolves into uninterrupted progression ([45] and [176]). Symptoms are associated with a pathogenic CNS-targeted autoimmune response sustained by leukocytes that invade brain and spinal cord parenchyma and accumulate in multifocal sclerotic plaques, the pathological hallmark of MS from which the disease gets its name [127]. After CNS entry, immune cells destroy myelin and oligodendrocytes and lead to axon degeneration and neuron loss. To date, diverse hypotheses have been raised to explain MS etiology, including genetic predisposition, activation of autoreactive immune cells, environmental factors and neuropathological conditions [191]. Immune-related molecules and lymphocytes are barely detectable in healthy brain, as the architectural and biological composition of the blood-brain barrier (BBB) protects the CNS from peripheral inflammation. The critical event in MS pathogenesis is instead represented by recruitment of lymphocytes into the CNS, which gain access across endothelial cells of the BBB through the activity of inflammatory molecules, including cytokines and adhesion molecules, synthesized by CNS inflammatory cells. The significant progress made in elucidating the molecules involved in immunopathogenesis of MS dramatically changed the therapeutic approach of this disease: molecules that specifically block adhesion receptors and thus inhibit leukocyte extravasation are now used in clinical trials ([204] and [219]). Thus, among the putative mechanisms that trigger the activation of the autoimmune reaction, inflammation is considered pivotal and microglia are thought to play a major role by up-regulating MHC class II molecules, inflammatory cytokines, reactive oxygen and nitrogen species; on the other hand, beneficial effects of microglia activation must be taken into account, such as myelin debris fagocytosis. This led us to propose inflammation as a candidate therapeutic target for MS within selected phases of the disease [150].

The EAE animal model—Major progress in the understanding of MS is due to the development of animal models where the biology of the disease as well as the response to specific pharmacological treatments can be observed. Experimental autoimmune encephalomyelitis (EAE) is the model system which mostly contributed to the understanding of the pathogenesis and the immune inflammatory mechanisms of human MS. EAE is induced by the immunization of susceptible mice with myelin proteins or peptides, such as myelin basic

protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG) in complete Freund's adjuvant. After 1–2 weeks, immunization induces activation of a delayed-type hypersensitivity, a type of reaction that is mediated by the activation of CD4+-Th1 and Th17 cells, that cross the BBB and secrete cytokines that both activate microglia and recruit circulating leukocytes ([12] and [75]).

Several studies highlighted the prominent role played by microglia activation in EAE. A study by Ponomarev et al. [188] recently investigated the timing of microglia activation in EAE by generating bone marrow chimera mice using MHC-mismatched donors, a model that allows to distinguish between resident microglial cells and monocyte-derived macrophages. These authors observed that the activation of microglia occurs before the onset of disease symptoms and infiltration of macrophages into the CNS. In addition, resting microglia were shown to undergo bystander activation, characterized by the upregulation of MHC II molecules, and were localized to the inflammatory lesions, which suggested a detrimental effect mainly ascribed to the secretion of neurotoxic molecules and self-antigens ([18], [114], [132], [229] and [235]).

Using transgenic mice carrying the selective ablation of proliferating microglia and undergoing experimental MS, it has been recently shown that the inhibition of microglia cells prevents the development and maintenance of the inflammatory CNS lesions [95]. Finally, a direct association between the intensity of microglia activation and EAE symptom gravity has been reported [2].

In both EAE and MS, inflammatory lesions classically occur in white matter, resulting in demyelination and axonal transection [236]. However, neuroimaging studies revealed microglia activation with minimal inflammatory cell infiltrates in proximity of cortical axonal transections [19]; this gray matter abnormality occurs surprisingly early and correlates much better with permanent disability, demonstrating that microglia activation in gray matter correlates with neuron loss and MS onset ([37], [52], [203] and [232]).

Estrogens and multiple sclerosis—Similar to other autoimmune diseases, MS is sexually dimorphic in that it occurs two times more frequently in women than in men [252]. This sexual dimorphism may be due to multiple factors; certainly gender-related differences in immune responsiveness are part of the cause, but sex hormones are likely to play a significant role ([65] and [111]) as indicated by a series of observations: *a.)* the first clinical symptoms of MS develop post-puberty; *b.)* increased levels of sex hormones produced during pregnancy are associated with a significant reduction in the severity of MS; *c.)* MS clinical symptoms are often exacerbated postpartum, a time characterized by significant alternations in sex hormone levels; *d.)* MS symptoms are altered also during the menstrual cycle ([1], [16], [46], [128] and [190]).

Although MS is more common in women, it affects men with a generally more rapid progression [255]. Also in the case of men, the male sex hormone, testosterone, was shown to affect microglial activation and to inhibit the development of EAE, inducing a Th2 bias in myelin basic protein-specific T-cells [51]. In view of the fact that the enzyme converting testosterone into estradiol, aromatase, is present in several cells and tissues it remains to be shown whether testosterone exerts its anti-inflammatory effect directly or through conversion in the female sex hormone. Gender differences in susceptibility to and severity of EAE have also been known for many years ([72], [163] and [246]).

The apparent conflict that women are more susceptible to the pathology than men, in spite of their capability to synthesize beneficial hormones like estrogens, might be ascribed to the fact that estrogens might be less potent natural inhibitors then testosterone. In addition, estrogen

effect on immune function might be biphasic: specifically, low doses of estrogens promote Th1 responses and increase cell-mediated immunity, while high doses result in increased Th-2 responses ([28] and [130]). Accordingly, women are more likely to develop a Th1 response to infective agents than men, so they are more susceptible to autoimmune diseases, except during pregnancy where women exhibit a pronounced Th2 response ([5], [184] and [252]).

Physiological or pharmacological fluctuations in estrogen levels have been recognised since a long time to play a regulatory role in EAE ([13], [109], [112], [121] and [151]). Oral administration of low doses of estrogenic hormones, 17beta-estradiol and ethinyl estradiol, drastically reduce the severity of EAE and this effect was reconciled with a decrease in the production of inflammatory Th1 cytokines (such as inteferon-γ (IFN-γ), Tumor Necrosis Factor-α (TNF-α), Interleukin (IL)-1 and IL-6), chemokines/receptors, while increasing the expression of anti-inflammatory Th2 cytokines (including IL-4, IL-5 and Transforming Growth factor-β3 (TGF-β3)) ([13], [109], [151] and [225]). This observation together with the fact that no infiltrating lymphocytes were found in the hormone-treated animals, led to the conclusion that estrogens protects mice from EAE by inhibiting the recruitment of T cells and macrophages into the CNS.

A further demonstration of estrogens as neuroprotective agents in EAE comes from the use of selective modulators of estrogen receptor (SERMs). Morales et al. [171] demonstrated that treatment with an ERα ligand is sufficient to recapitulate the estrogen-mediated protection in EAE, consistent with a report by Elloso et al. [70] that demonstrated that treatment with an ERα, but not an ERβ, ligand could reduce acute EAE disease severity. The degree of preservation of neuronal integrity in the gray matter of estradiol and ERα ligand-treated mice with EAE in this study was striking, and this has major implications for neurodegenerative changes that occur "beyond the lesion" in EAE and possibly MS.

Two cellular targets have been proposed to mediate estrogen protective activity in MS and EAE, namely T-cells and brain inflammatory cells. Estrogens are able to shift the T-cell population towards a Th2 phenotype, an activity also confirmed in pilot clinical studies ([48], [84], [213] and [216]) and to influence a subpopulation of Th cells, named T-regulatory cells ([186] and [228]). On the other hand, microglia and endothelial cells have probably a more significant role in estrogen action; using irradiation bone marrow chimeras it has been recently shown that the effect of estradiol on clinical EAE and CNS inflammation was not dependent on ERα expression in the peripheral immune system but was conferred by ERα expression on CNS resident cells, namely endothelial and microglial cells ([81] and [187]). It is thus important to fill the gap in the characterization of estrogen signalling in these resident brain cells and in assessing its relevance in estrogen-mediated neuroprotective activity in EAE.

3.2 Alzheimer’s disease and neuroinflammation

Alzheimer's disease (AD) is a progressive neurodegenerative disorder; its pathological hallmarks include extracellular senile plaques mainly made of the amyloid β (Aβ) peptide, and neuronal anomalies including neurofibrillary tangles composed of hyperphosphorylated forms of the microtubule associated protein tau (MAPT); these specific pathologic features are also associated with dystrophic neurites and by reactive astrocytes and activated microglia ([22] and [199]). Although the mechanisms leading to progressive neuronal death in brain are still under investigation, several lines of evidence sustain the amyloid hypothesis, which postulates that abnormal cellular production and deposition of Aβ peptide is a relevant trigger of neurodegeneration in AD [249]. In fact, genetic studies in hereditary AD identified mutations in the genes encoding APP, presenilin (PSEN1) and PSEN2, each associated with increased production of Aβ. Indeed, the well known risk factor apolipoprotein E ε4 allele is shown to control the clearance of Aβ in brain ([9] and [222]).

The Aβ peptide is derived from the two-step enzymatic processing of amyloid precursor protein [APP] in which β-secretase [BACE] cleaves APP to release the N-terminus of Aβ, followed by the cleavage by γ-secretase protein complex to release the C-terminus of Aβ ([87] and [241]). Thus, the initial cleavage of APP by BACE is critical for the formation of the 40 or 42 aminoacids-long Aβ peptides ($A\beta_{1–40}$ and $A\beta_{1–42}$), which deposit as fibrillar amyloid in the senile plaques; it has been shown that BACE activity increases with age and it is elevated in AD brains ([100] and [138]). Amyloidogenic peptides were shown to play a major role in brain neurotoxicity, however the molecular mechanisms remain to be clearly defined.

Recent evidence suggests that inflammatory processes play an active role in AD; epidemiological studies reported that the use of nonsteroidal anti-inflammatory drugs is associated with marked reduction in the risk of AD ([107], [156], [157], [221] and [227]). Following this initial observation, additional reports were published that witnessed the involvement of neuroinflammation in AD pathogenesis and progression. In fact, a series of proinflammatory molecules, including proteins of the complement system, cytokines and chemokines and their receptors, were found to be increased in the brain and cerebrospinal fluid (CSF) of AD patients ([76] and [257]). Polymorphisms in inflammatory genes were also found in association with AD [32].

The involvement of microglia in neuroinflammation associated with AD has also been described [116]. Resting microglial cells can be activated by Aβ in brain, they migrate and surround the region of compact Aβ deposits, where they help removing Aβ ([7], [66], [74], [145], [154] and [250]). These data argue in favour of an essential role of microglia cells. In chronic inflammatory processes that may ultimately lead to neuronal degeneration.

Animal models of Alzheimer's disease—The identification of genetic polymorphisms associated to hereditary forms of AD led to the generation of transgenic animals modelling the human disorder. These transgenic mice produce high levels of human Aβ40 and Aβ42 peptides and develop amyloid deposits in the brain which are very similar to those seen in the human AD brain and thus represent a unique tool in the study of this condition. The first animal models that developed amyloid plaques were generated by integrating in the mouse genome the gene encoding human APP containing mutations associated with early-onset AD ([77], [102] and [217]). These mice develop amyloid plaque pathology and selective cognitive deficits, pathologic features that dramatically accelerate in the next generation of AD animal models generated by crossing APP mutant animals with mice carrying the mutated PSEN1 gene ([20], [64] and [99]). Plaque pathology in these models is associated with microgliosis and astrogliosis. Despite the robust amyloid deposition observed in APP and PSAPP transgenic mice and evidence for progressive synaptic degeneration and dysfunction, none of these models show neuron loss or formation of intraneuronal fibrillary tangles. On the other hand, mouse models expressing wild type or mutant MAPT gene have been generated that recapitulate most of the features of human neurofibrillary pathology and significant neuronal loss ([4], [137], [207] and [265]). Further crossings among AD transgenic models have allowed to reach the conclusion that, although a mouse model that recapitulates all aspects of AD has yet to be obtained, amyloid deposition can accelerate or initiate the formation of neurofibrillary tangles while MAPT accumulation or other secondary events initiate neurodegeneration ([159], [177] and [178]).

The observation that activated microglia are present at amyloid deposits in human AD and in animal models of this disease suggested that it might play a pathogenic role as a result of their chronic activation, although the presence of cytoplasmic Aβ granules in plaque-associated glia and microglia suggest that these cells participate in the clearance of Aβ ([7], [43], [66], [74], [126], [145], [154], [181], [217], [250], [256], [259] and [261]). However, this hypothesis is hard to prove using experimental models of this disease in which many pathological features

occur, namely amyloid deposition, neurofibrillary tangle formation, inflammation, neuritic and neuronal loss, synaptic and neuronal dysfunction, vascular alterations [198].

As an example of AD models, the APP23 transgenic mice overexpress the human APP_{751} with the familial Swedish AD double mutations at positions 670/671 [223]; in this model, amyloid plaques are first observed at 6 months of age and then plaque size and number increase dramatically with aging. The congophilic, dense-core Aβ deposits show many characteristics of human AD plaques such as enlarged dystrophic neurites [30]. Similar to AD, vascular amyloid is also present in aged APP23 animals [29]. Compact amyloid deposits are associated with microglia cells showing a characteristic activated morphology [217] and with reactive astrocytes [223].

A step forward in understanding the role of microglia in amyloid pathology derived from the comprehension of the molecular details of microglia activation by Aβ. The so-called pattern recognition receptors (PRRs) are a heterogenous class of proteins that are constitutively expressed by macrophages/phagocytes to monitor the extracellular environment. Activation of PRRs leads to microglia reactivity, a process that could be both beneficial in removing toxic signals as well as deleterious in producing and enhancing toxicity. Brain and microglial up-regulation of PRRs members has been observed in human and experimental AD ([3], [68], [21] and [260]). The Aβ peptide was shown to activate microglia cells through the interaction with specific PRR: *a)* scavenger receptors, including scavenger receptor class-A (SR-A), SR-B1 and CD36, that mediate Aβ endocytosis and induce ROS production ([47] and [67]); *b)* macrophage receptor with collagenous domain (MARCO), a scavenger receptor that mediates adhesion of Aβ to microglia and the cytoskeleton rearrangements induced by this peptide [85]; *c)* the receptor for advanced glycation endproducts (RAGE), a member of the immunoglobulin superfamily, responsible for the induction of the inflammatory response stimulated by Aβ ([6], [144] and [260]).

Intensive studies further addressed the role of neuroinflammation in AD pathogenesis and progression. In addition to resident microglia, mononuclear cells that are recruited from the blood are key players in AD pathogenesis; in fact, depletion of this cell pool or ablation of the receptor protein that recruits monocytes into the brain, accelerated Aβ accumulation and animal mortality ([69] and [214]). On the other hand, anti-inflammatory agents such as COX-1 inhibitors induced a dose-dependent reduction in pathology in humans and transgenic mouse model of AD [156]. Interestingly, a contribution of T and B cell-mediated immune responses to the inflammatory processes and to the plaque pathology seems unlikely in both human and experimental AD.

Estrogens and Alzheimer's disease—The hypothesis of a potential role of estrogens in AD has been put forward by a number of epidemiological, retrospective studies that have demonstrated an inverse correlation between estrogen replacement therapy and incidence of AD ([15], [92], [118], [179], [180] and [230]). These observations have been challenged by a recent randomised clinical trial that showed increased risk of dementia in hormone therapy (HT)-assigned women participating at the Women Health Initiative Study ([71] and [195]). Despite these initial claims, a more in depth analysis of the WHI data, taking under consideration the time between menopause onset and HT assumption, showed beneficial effects of estrogens when therapy is initiated early after menopause, while the detrimental effects were associated with a treatment started several years after menopause [196]. Supporting this view, a well focused study carried out on women that underwent surgical removal of the ovaries before menopause clearly demonstrated that oophorectomy was associated with an increased risk of cognitive impairment and dementia [197]. This suggests that more and more well aimed studies are necessary in order to be able to reach a consensus on the effects of estrogens on brain health.

Indeed, most of the well controlled studies carried out in experimental animals are supportive of a protective effect of estrogens against neuronal loss. For instance, aromatase gene knockout mice in which estrogen synthesis is absent, showed enhanced hippocampal neuronal loss in response to neurotoxins compared with WT mice [8]. Interestingly, brain estradiol levels and aromatase expression are significantly reduced in the brains of women with AD [262]. The view of brain estrogen deficiency as a risk factor for developing AD pathology is consistent with genetic studies showing an association between variants of aromatase gene and the risk for several diseases, including AD ([106] and [215]).

A large body of experimental evidence demonstrates that estrogens protect against Aβ neurotoxicity. Estradiol increases APP expression in neuronal cells ([35], [110] and [258]) and reduces Aβ peptide production while enhancing its clearance ([36], [139] and[258]). A modification of Aβ levels was induced by estradiol treatment in the Tg2576 AD model [269]. Recent data from a transgenic animal model developed by Yue et al. that overexpresses APP and lacks the aromatase enzyme, the APP23/$Ar^{+/-}$ mice, show an earlier onset of plaque formation compared to ovariectomized APP23 mice [262]. In this model it was also found that BACE protein expression and activity, as well as $A\beta_{40}$ and $A\beta_{42}$ levels, were elevated in the brains of APP23/$Ar^{+/-}$ mice as young as 6 months. Thus, the early-onset AD neuropathology in APP23/$Ar^{+/-}$ mice associated with brain estrogen deficiency may be mediated by increased BACE activity and accelerated Aβ production. In a very recent study, Carroll et al used the triple transgenic mouse model of AD to investigate the individual and combined effects of estrogens and progesterone on different pathological features. Ovariectomy significantly increased Aβ accumulation and worsened memory performance, while chronic estradiol treatment prevented these effects. In addition, progesterone administration reduced tau phosphorylation, while when added in combination with estradiol prevented the effect of estrogen on Aβ accumulation but not on behavioural performance [33].

Taken together, these results suggest that brain estrogen deficiency accelerates AD pathologic features and that the estrogenic therapy may be beneficial in reducing the risk of AD.

Our laboratory provided evidence to demonstrate the ability of estradiol to control brain inflammatory cells reactivity ([242] and [244]). We analysed the effects of the deprivation of endogenous estrogens or of HT on microglia reactivity in the APP23 mice [243]. We first observed that the number of plaques that were associated with reactive microglia increased with age, suggesting that the inflammatory reaction was indeed progressing in parallel with the disease. Interestingly, ovariectomy clearly accelerated microglia activation surrounding Aβ plaques, whereas estradiol replacement delayed this process, thus indicating that estradiol influences the neuroinflammatory process that is associated with the APP genetic defect. In parallel, we showed that estradiol is able to down-regulate inflammatory genes expression in brain: the increase in the mRNA for macrophage/monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2) and TNF-α induced by LPS injection in the cerebral ventricles was clearly restricted by hormone administration. Most interestingly, SR-A expression induced by Aβ in macrophage cells was inhibited by estradiol pre-treatment, providing a potential mechanism for hormone inhibitory activity on microglia responsiveness observed in the APP23 mouse model [243].

These data clearly support a role of estrogen anti-inflammaotry action as contributing factor to estrogen therapy prevention of AD through direct regulation of resident microglia to inhibit chronic inflammation associated with AD. However, other cellular targets may underscore estrogen neuroprotective activity in the CNS: i) neurons, through hormone anti-apoptotic and neurotrophic actions; ii) neural stem cells, by inducing their proliferation; iii) astroglial cells, by increasing their potential for secreting neuroprotective molecules or decreasing the production of neurotoxic agents; iv) endothelial cells, on which estrogens act to reduce

adhesion molecule expression and other factors that recruit circulating leukocytes ([146] and [189]).

3.3 Parkinson's disease and neuroinflammation

Parkinson's disease is a neurodegenerative disease characterized by a progressive loss of dopaminergic neurons in the substantia nigra (SN) and by intracellular inclusions of aggregated α-synuclein, known as Lewy bodies. It is believed that a combination of environmental and genetic factors predisposes to disease onset and severity. The genetic defects associated with PD are due to mutations in proteins that serve disparate functions yet converging on impaired α-synuclein signalling and clearance [73]; on the other hand, several toxins are known to specifically damage dopaminergic (DA) neurons and lead to PD-like symptomatology through recently characterised signalling pathways [17].

The selective loss of DA neurons is likely due to the increased vulnerability of these cells to oxidative stress, as these neurons have lower levels of glutathione compared with other cell types, and are thus more responsive to the effects of mitochondrial dysfunction ([97] and [143]). In addition to oxidative stress also other mechanisms have been proposed to be involved in selective DA neuron degeneration in PD, including excitotoxicity, intracellular calcium and metal ion rise, neurofibrillary tangle formation and disruption of the cytoskeletal transport [113]. More recently, neuroinflammation and microglial activation have been implicated in the neurodegenerative process in PD, as initially suggested by McGeer et al. [154] and then by several authors ([79], [90], [96], [98], [104], [105], [108], [149] and [169]). In fact, studies accumulated over the last two decades have clearly indicated the presence of an abnormal glial response in postmortem nervous system of PD patients. The positive correlation between antecedent brain injuries, such as trauma or exposure to infectious agents, and PD development implies that the brain inflammatory response to these noxious events, and specifically microglial activation, may play a critical role in PD pathogenesis [141]. Accordingly, other authors detected the expression of pro-inflammatory molecules, such as TNF-α, IL-1β and IFN-γ, as well as iNOS and Cox-2 and the accumulation of reactive oxygen and nitrogen species in the nervous system of PD patients ([98], [103] and [125]), further supporting the theory that PD is associated with the chronic activation of the brain inflammatory response. These inflammatory molecules, along with factors released from the dying dopaminergic cells, seem to amplify and sustain neuroinflammation as well as neural cell toxicity leading to a slow and irreversible destruction of SN dopaminergic neurons. In agreement with McGeer's hypothesis on the role of activated glial cells and brain inflammation in PD, administration of nonsteroidal anti-inflammatory drugs were shown to reduce the risk of PD ([40], [209] and [247]), suggesting that inhibitors of inflammation are promising therapeutics for PD.

Animal models of Parkinson's disease—The dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine [MPTP] is known to induce parkinsonism in humans, primates, and mice ([27], [91], [133] and [135]). MPTP is converted by astrocytes to the metabolite 1 methyl-4-phenylpyridinium [MPP^+], a substrate of the DA transporter ([41] and [42]). MPP^+ thus accumulates in dopaminergic neurons where it inhibits the mitochondrial complex I of the electron transport chain, resulting in ATP depletion and subsequent inability to release sufficient amounts of dopamine and ultimately leading to apoptosis [233]. However, Lewy bodies were not observed in the brain of PD patients exposed to MPTP, revealing a significant difference between MPTP-induced neurotoxicity and PD itself despite the considerable clinical similarities [134].

A precise understanding of how MPTP induces DA neuron degeneration is still lacking; in addition to what described above, it has been shown that pre-treatment with N-methyl-D-

aspartate [NMDA] receptor antagonists can protect SN neurons, thus linking the effect of MPTP with excitotoxicity [240].

Recently, the induction of neuroinflammation received much attention as a key pathway involved in MPTP-induced pathogenesis and progression ([10], [165] and[182]). Langston et al. found that in post-mortem examination of brains from humans exposed to MPTP activated microglia were present up to 16 years after exposure, indicating a protracted inflammatory response [134]. These observations are strongly indicative of a process by which an ongoing stimulus could lead to disease progression long after the initial toxic insult. These findings are supported by studies in the nervous system of primates, which show that activated microglia and dopaminergic cell loss continue to occur years after exposure to MPTP [158].

Further studies showed that chronic activation of microglia by MPTP leads to their clustering around DA neurons and transformation in phagocytic cells ([11] and [23]).

How does MPTP-stimulated neurons activate microglia? The combination of released factors and expression of surface adhesion molecules by MPTP-treated DA neurons recruits and activates surrounding microglia and leads to a progressive and irreversible neuronal cell death, which is worsened by the release of chemoattractants by the dying neurons to induce even greater infiltration of the region by activated microglia. Recent studies provided molecular details to the understanding of the neuroinflammaotry component in PD. It has been shown that the products secreted by damaged neurons ([253] and [120]) aggregated alpha-synuclein or environmental toxins such as LPS are recognised by the macrophage antigen complex 1, Mac-1, a PRR expressed on microglia cells; in turn, Mac-1 activation is crucial for activation of NADPH oxidase, a membrane-bound enzyme that catalyses the production of superoxide anions, which are released in the extracellular space, and generates intracellular ROS, well known triggers of the inflammatory response ([18], [123], [224] and [267]). NADPH oxidase is associated with neurodegenerative disorders and neuronal damage; it is activated in the brains of patients with PD [254].

Through these evidence it appears that microglia activation has a detrimental role, as it results in the release of ROS by microglia in the extracellular space. Particular attention received the molecular mechanism of action of LPS on dopaminergic neurodegeneration. LPS has no known direct toxic effects on neurons but is a powerful tool for inducing the release of a host of neurotoxic factors through the direct activation of microglia. The substantia nigra is reported to be particularly susceptible to LPS-induced injury because it is rich in microglia [122]. LPS induces a rapid activation of microglia and a delayed, progressive and selective destruction of nigral dopaminergic neurons both *in vivo* and *in vitro* ([78], [79], [80]). Finally, using mice carrying a deletion in the gene coding for NADPH oxidase, one major source of intracellular ROS, or in Mac-1 it has been possible to clearly demonstrate that the production of ROS by LPS-activated microglia is directly toxic to neurons as well as the secretion of proinflammatory molecules, which foster neurodegeneration as well ([183], [192], [254], [266] and [267]).

Finally, anti-inflammatory drugs, such as cyclooxygenase inhibitors, statins or pioglitazone, were shown to protect neurons against degeneration induced by MPTP ([55], [210] and [231]), further providing evidence to indicate the role of neuroinflammation in PD neurodegeneration.

Estrogens and Parkinson's disease—A number of epidemiological studies reported that the incidence and prevalence of PD is higher in men than in women ([56] and [131]). Post-menopausal estrogen deficiency has been reported to cause a worsening of Parkinson-related symptoms, whereas the severity of symptoms in women with early PD is diminished by the use of estradiol [206]. Furthermore, it has been shown that estrogen replacement therapy lowers

symptom severity in women with early PD not yet taking L-Dopa [208] and improves motor disability in parkinsonian postmenopausal women with motor fluctuations [238]. Association between ER gene polymorphism and PD has been reported [251]. Rocca et al. recently reported that both unilateral and bilateral oophorectomy performed prior to menopause may be associated with an increased risk of parkinsonism and the effect may be age-dependent [197]. These data are suggestive of a beneficial protective role of estrogens.

Many experimental studies examined the responsiveness of DA neurons to estrogens and showed that estradiol levels induces DA synthesis and release, as well as DA neurons differentiation ([59], [60], [82], [152] and [172]). Importantly, MPTP caused greater DA depletion in male compared with female mice [58]; moreover, treatment with estradiol prevented the reduction in DA concentrations and the activation of glia in the striatum of animals treated with MPTP ([31], [58], [170] and [237]). The essential role of estrogens in maintaining the integrity of DA system in the CNS has also been extended to primates [136]. This evidence suggested a new treatment strategy for patients with PD and encouraging results are being obtained from pilot clinical studies assessing HT safety and effectiveness in PD [140]. Although a direct evidence for a role of estrogen-microglia signalling in PD models is still lacking, clear evidence suggests that estrogen signalling in these cells prevent microglia activaton induced by a number of endogenous or environmental factors ([26], [242] and [244]). It is presumed that the complementary action of estradiol on neurons, astrocyte and microglia may provide beneficial outcome and represents a potential pharmacological target for delaying or preventing PD symptoms.

4. The mechanism of estrogen action in neuroinflammation

As previously described, estrogens are believed to act in microglia via the activation of the endogenous estrogen receptors (ER). The two ER proteins recognised so far, ERα and ERβ, are intracellular proteins which activate genomic as well as nongenomic effectors in neural cells [146]. Through the use of the estrogen receptor antagonist ICI 182780 we and others initially ascribed hormone action in microglia to the activation of endogenous ERs, since this molecule was able to block the effect of estradiol ([24], [25], [142] and [244]). Using ER-null mice several reports described the selective involvement of ERα in the anti-inflammatory and neuroprotective activity of estradiol against neuroinflammatory and vascular pathologies of the brain ([63], [81], [187] and [242]). Despite the fact that ERβ has been shown to be expressed widely in the CNS in adult mice ([162] and [168]), it appears that this receptor isoform is not involved in mediating the protective effect of estrogens in neuroinflammatory diseases. Yet, both ERα and ERβ are involved in the control of inflammation by estradiol, depending on the tissue involved and on the signal utilized [89]. Whether one of the two receptors prevails, reduces, potentiates or does not influence the other isoform in inflammatory cells still remains to be defined.

Basic research in estrogen signalling also provided another relevant key point in estrogen action, that is cell-specificity. Divergent effects of estrogens have been reported for T cell activation [49] as compared with microglia and astroglia based on different hormone concentrations ([61] and [83]). Additionally, expression of iNOS is reduced in certain cell types, including microglia ([26], [50], [205], [244] and [263]) while hormone actually increases the expression of endothelial and neuronal subtypes of NOS ([193] and [205]). Thus, it is important to fully characterize the signal transduction mechanisms of estrogen signaling in different cell types of the CNS and the relative contributions of each of the two isoforms of estrogen receptor involved, so that appropriate therapeutic agents can be devised.

Selective ER modulators

Since their original description ([164] and [218]) ERα and ERβ selective modulators (SERMs) have been employed to dissect the relative contribution of each ER subtype and to obtain more potent responses devoid of toxic effects. The ERα selective ligand propyl pyrazole triol (PPT) provides neuroprotection and anti-inflammatory activities in brain in experimental models of neurodegenerative diseases, including ischemia [166], MPTP-induced neurotoxicity [53] and EAE ([70] and [171]). The *in vitro* activity of PPT has been studied in neuronal cells [268], while our preliminary data demonstrate a direct anti-inflammatory activity of this ligand in microglia (unpublished results). On the other hand, ERβ selective agonists produced neuroprotective effects in global ischemia ([34] and [166]) and EAE [234], while being inactive in the MPTP-induced dopamine depletion model [53]. Recent work by Tiwari-Woodruff et al. demonstrated that the ERβ selective agonist is also able to protect neurons in advanced stages of the EAE model through a strong neuroprotective action without altering the inflammatory component [234], suggesting that selective activation of ERs can trigger distinct, beneficial effects in the CNS. Future research in this field will lead to the experimental exploitation and possibly to the therapeutic application of SERMs in selected human diseases, in that they would permit to exploit only the benefits deriving from hormone therapy while reducing the undesired side effects.

Molecular aspects of estrogen action in microglia

In an attempt to examine the specific mechanism of estrogen action in brain inflammatory cells we recently identified a novel mechanism of estrogen action that results in the inhibition of inflammatory gene transcription. We demonstrated that the intracellular machinery that drives the transport of proteins, and in particular the transcription factor p65, from the cytoplasm to the nucleus is a target for estrogen activity in microglia and macrophage cells [83]. p65 is a member of the NF-κB family of transcription factors, which are confined to the cytoplasm of unstimulated cells and move from this compartment to the nucleus upon inflammatory stimuli, such as LPS, with a rapid and massive translocation; in the nucleus, these factors induce inflammatory gene transcription through the binding to DNA responsive elements in the promoter of target genes. In our study we observed that microglia and macrophage cells treated with estradiol before LPS resulted in the persistent cytoplasmic localization of p65. We ascribed this effect to the interference with the microtubule-dependent intracellular transport of NF-κB ([115] and [200]), which results in reduced nuclear availability of NK-FB and thus in decreased transcription of NF-κB target genes, such as MIP-2 or Ik-Bα. Estrogen action was mediated specifically by ERα and through the activation of the PI3K. Of particular notice is the fact that estradiol does not modify IKKβ activity nor Iκ-Bα degradation, which are known targets of anti-inflammatory drugs, suggesting a unique mechanism of action of this female hormone among anti-inflammatory endogenous signals and drugs [Figure 2] [83]. We believe that these data provide a novel background for the identification of innovative targets and pharmacological interventions aimed at preventing inflammation.

The timing hypothesis

As discussed above, post-menopausal estrogen deficiency is a key event in the pathogenesis of a number of neurodegenerative diseases in women. However, the potent activity of exogenous estrogens in experimental models is paralleled by controversial results in humans ([211] and [212]). Secondary analyses of recent randomized clinical trials, that originally raised controversies among the scientific community as to the risk/benefit ratio of HT ([86], [160] and [239]), helped to consolidate a novel hypothesis on the efficacy of hormone therapy [202]; it is now hypothesized that HT should be started in early menopause, as a preventative treatment of relatively healthy women, in order to avoid the negative consequences of hypoestrogenicity *per se* [93]. In fact, observational and randomized clinical trials show that

HT does not improve memory or intellectual functions in women already affected by mild to moderate AD ([71], [173] and [201]), whereas it delays disease onset when administered in healthy perimenopausal women ([101], [118], [202] and [230]). Accordingly, a very recent study demonstrated that surgical menopause is associated with an increased risk of cognitive impairment and dementia in women [197]; novel directions in correctly evaluating specific cognitive functions have also been formulated, since the effect of female steroid hormones on cognitive activities varies across cognitive domains [196]. Thus, it appears that full benefits from HT are achieved through correct timing of hormone assumption. Based on this knowledge, trials are now being designed that will consider the disease duration and menopausal status of the subjects ([147] and [161]).

Substantial experimental data support the hypothesis that hormone anti-inflammatory activity is beneficial if estrogen administration precedes the inflammatory burst and when it is given shortly after ovary removal. In fact, estradiol does not alter the inflammatory signaling cascade in microglia if it is administered after inflammatory stimuli ([26], [83] and [242]); in addition, a prolonged hormonal deprivation affects estrogen protective activity in ischemia and causes a null or even opposite response to exogenous hormone administration [226]. Collectively, the experimental evidence indicate that the efficacy of estrogenic molecules as anti-inflammatory agents is also confined in a therapeutic window and that their use should be considered only as preventive pharmacological strategies.

5. Conclusions

The evidence thus far clearly indicates a prominent role of estrogen anti-inflammatory action in protecting the CNS against neurotoxic stimuli. Experimental data show that receptor selectivity, time frame and concentration of hormone, as well as cell-specific molecular partners are key features in the efficacy of estrogens to control microglia and brain inflammation. It is worth underscoring that microglia activation associated with neurodegenerative processes is also endowed with beneficial effects, as microglia cells were shown to produce trophic and survival factors and to eliminate through phagocytosis the noxious material accumulated in the extracellular space ([119] and [148]). Identifying the molecular mechanisms of estrogen action will elucidate the conditions regulating the beneficial *vs* detrimental pathways can be separately activated, leading to the design of more selective regulatory agents that inhibit the deleterious effects while maintaining the protective role played by these immune cells in the neural tissue. Finally, future research could lead to identification of the most appropriate and selective estrogenic drugs to be used in post-menopausal as well as fertile female patients eligible for HT.

Acknowledgments

This work was supported by grants from the European Community (“EWA” LSHM-CT-2005-518245 to AM and EV; “DIMI” LSHB-CT-2005-52146 to AM), the NIH (RO1-AG027713-01 to AM) and the Italian Ministry for University and Scientific Research (COFIN 2006065483_003 to EV).

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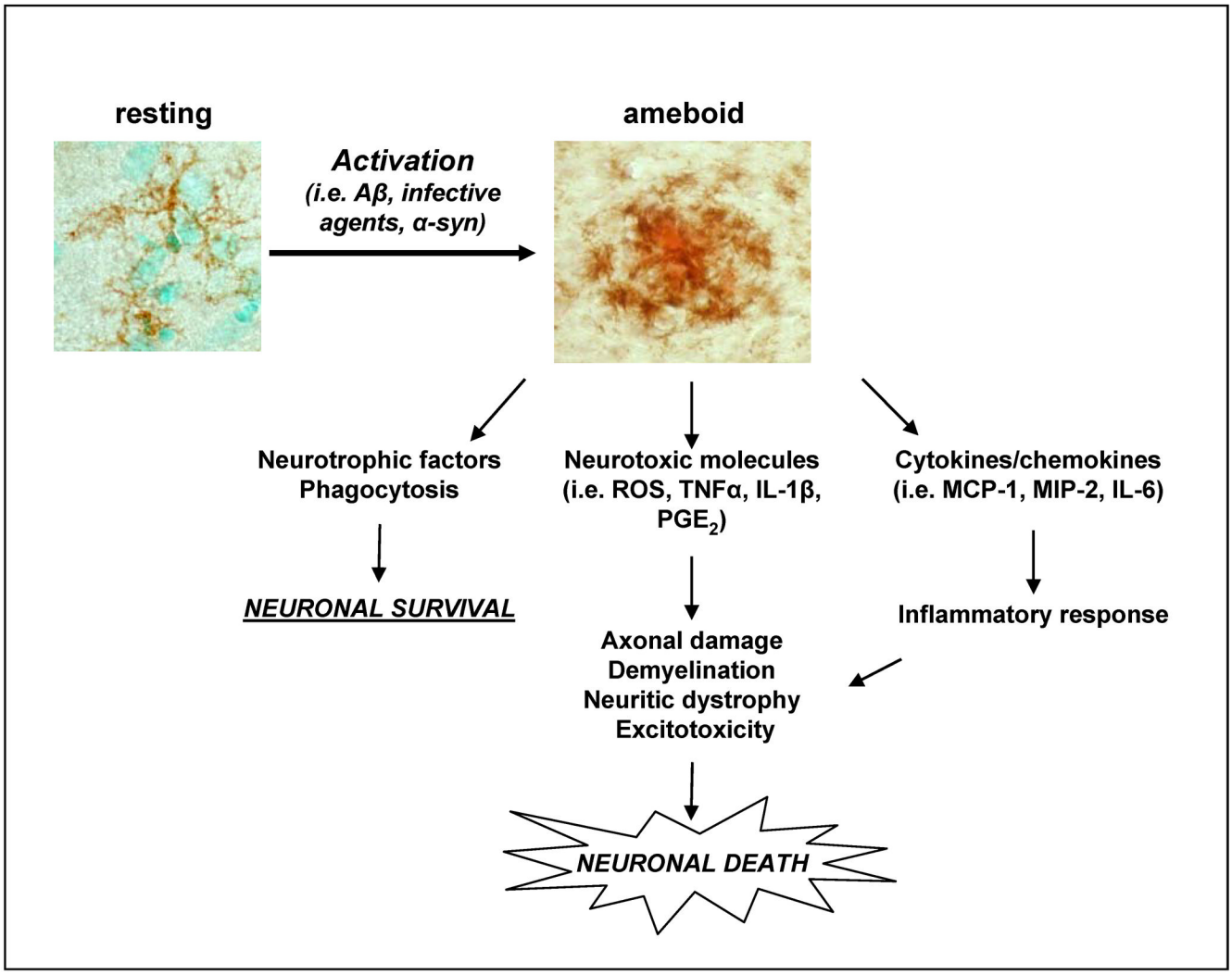

Figure 1. Microglia activation and neural cell loss

Activation of microglia causes the secretion of short-lived diffusible molecules, such as reactive oxygen species (ROS), that produce an oxidative burst that is directly toxic to surrounding cells. In addition, peptides and inflammatory mediators are produced by activated microglia to communicate the ongoing local reaction to the periphery; circulating inflammatory cells are attracted by these molecules to the injured site and further sustain the local inflammatory reaction. Secretion of neurotrophic factors, as well as elimination of noxious material from the extracellular space through phagocytosis are also key features of microglia activation, which have instead beneficial consequences for brain health.

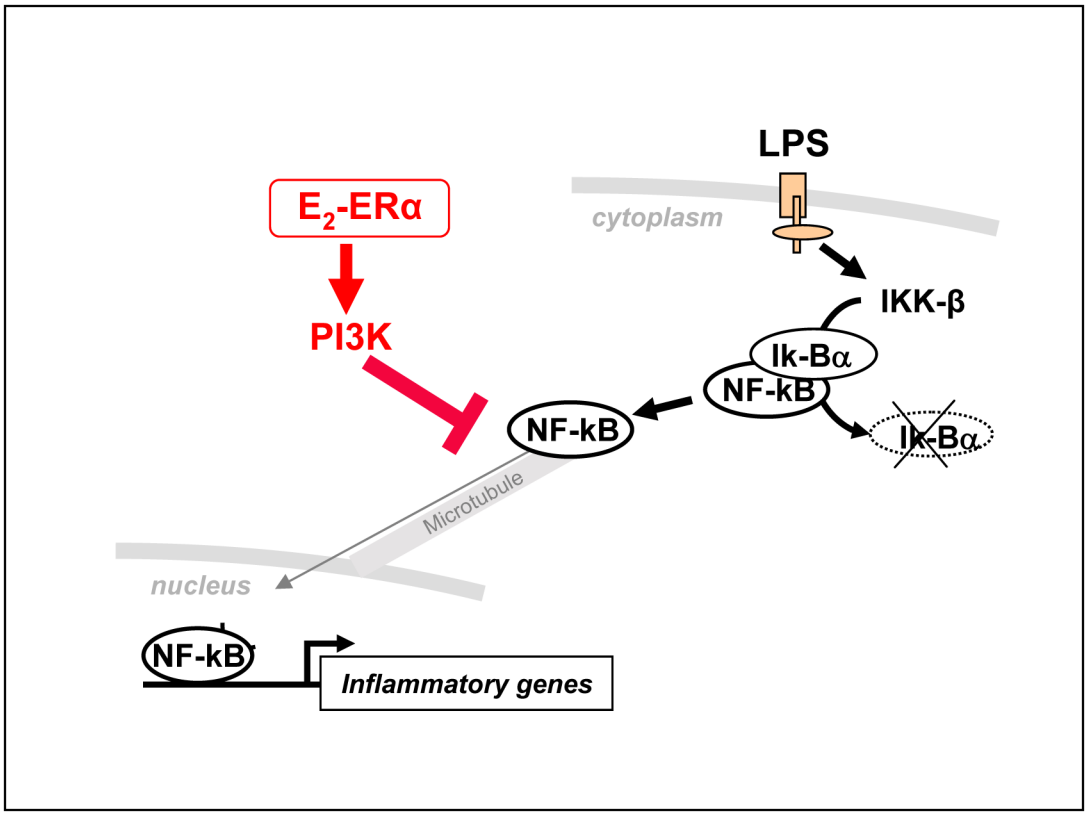

Figure 2. Estrogen anti-inflammatory action

Schematic representation of the mechanism of action of estradiol in microglia proposed by our lab. The cytoplasmic activity of estrogen-activated ERα, including PI3K induction, inhibits the intracellular transport of NF-kB that is induced by inflammatory stimuli, such as LPS; this leads to reduced synthesis of inflammatory mediators and microglia activation.