REVIEW

Neuroactive steroids, their metabolites, and neuroinflammation

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Abstract

Neuroinflammation represents a common feature of many neurodegenerative diseases implicated both in their onset and progression. Neuroactive steroids act as physiological regulators and protective agents in the nervous system. Therefore, the attention of biomedical research has been recently addressed in evaluating whether neuroactive steroids, such as progestagens, androgens, and estrogens may also affect neuroinflammatory pathways. Observations so far obtained suggest a general anti-inflammatory effect with a beneficial relapse on several neurodegenerative experimental models, thus confirming the potentiality of a neuroprotective strategy based on neuroactive steroids. In this scenario, neuroactive steroid metabolism and the sophisticated machinery involved in their signaling are becoming especially attractive. In particular, because metabolism of neuroactive steroids as well as expression of their receptors is affected during the course of neurodegenerative events, a crucial role of progesterone and testosterone metabolites in modulating neuroinflammation and neurodegeneration may be proposed. In the present review, we will address this issue, providing evidence supporting the hypothesis that the efficacy of neuroactive steroids could be improved through the use of their metabolites.

Journal of Molecular Endocrinology (2012) **49,** R125–R134

Introduction

Neuroactive steroids act as important physiological regulators of CNS functions (Melcangi *et al.* 2008, 2011, Panzica *et al.* 2012). Moreover, as demonstrated in experimental models of several neurodegenerative disorders, the administration of neuroactive steroids is able to favor several protective/reparative processes like inhibition of neuronal death, promotion of neurogenesis, and myelination, as well as reduction of neuroinflammation (Brinton & Wang 2006, Garcia-Segura & Balthazart 2009, Melcangi & Garcia-Segura 2010, Melcangi *et al.* 2011, Kipp *et al.* 2012, Panzica *et al.* 2012, Schumacher *et al.* 2012). Intriguing is the modulation of this last process. Neuroinflammation is shared by a number of pathologies, ranging from neurodegenerative to psychiatric diseases (Glass *et al.* 2010, Tansey 2010, Tansey & Goldberg 2010, Wee Yong 2010, Wuwongse *et al.* 2010, Meyer *et al.* 2011) and represents an early response to any perturbation of the CNS physiology leading to dysfunction and degeneration when deregulated (Block *et al.* 2007). Thus, the possibility to modulate this phenomenon becomes valuable in terms of preventing disease progression.

An emerging issue in the field of neuroactive steroids is the role of progesterone (PROG) and testosterone metabolites. In particular, the observation that metabolites are i) more active than the precursor molecule (Melcangi *et al.* 2008), ii) appear to be necessary for some of the effects exerted by PROG or testosterone (Ghoumari *et al.* 2003, Giachino *et al.* 2003, 2004, Ciriza *et al.* 2004, 2006, Djebaili *et al.* 2004, He *et al.* 2004, Pesaresi *et al.* 2010*a*, Sun *et al.* 2012), and iii) their synthesis is impaired in CNS diseases (Labombarda *et al.* 2006, Meffre *et al.* 2007, Caruso *et al.* 2008, 2010, Giatti *et al.* 2010, Naylor *et al.* 2010, Pesaresi *et al.* 2010*b*, Melcangi *et al.* 2012) suggest that these molecules might share a higher therapeutic impact than classical hormones like PROG and testosterone.

The present review will recapitulate what is known about the anti-inflammatory properties of neuroactive steroids, with a particular focus on PROG and testosterone metabolites.

0952–5041/12/049–R125
DOI: 10.1530/JME-12-0127
Online version via http://www.endocrinology-journals.org

Neuroactive steroids: state of the art

The nervous system is a well-known target for the endocrine effects of hormonal steroids coming from peripheral steroidogenic glands. However, the nervous system is also controlled in a paracrine and autocrine manner by steroids directly synthesized by neurons and glial cells, named neurosteroids (Baulieu 1998). More recently, this concept was expanded into the neuroactive steroid family, including hormonal steroids, neurosteroids, and synthetic steroids that are able to regulate several neuronal functions (Melcangi *et al.* 2008).

Synthesis and metabolism of neuroactive steroids occur in neurons and glial cells (Garcia-Segura & Melcangi 2006, Melcangi *et al.* 2008, Panzica & Melcangi 2008, Pelletier 2010). Steroidogenesis is a process highly compartmentalized in a sequence of reactions, which implies as a first step the translocation of cholesterol from the cytoplasm to the mitochondrial membrane (Fig. 1). This is a limiting step hormonally controlled and mediated by the StAR (Lavaque *et al.* 2006*a*,*b*) and 18 kDa translocator protein (Papadopoulos *et al.* 2006). In the mitochondria, the enzyme P450 side chain cleavage (P450scc) converts cholesterol into pregnenolone (PREG), which is further transformed into PROG or DHEA in the endoplasmic reticulum (Melcangi *et al.* 2008). Notably, these molecules exert effects on the CNS *per se*, but may undergo metabolic transformations leading to the formation of neuroactive metabolites. Due to their lipophilic structure, neuroactive steroids move from one cell to another. This greatly impacts their metabolism that will be ruled by the enzymatic repertoire expressed in different cell types. For example, DHEA can be converted into androstenediol, and subsequently into testosterone, or into androstenedione in all the cells of the CNS (Melcangi *et al.* 2008). In neurons, androstenedione, as well as testosterone, may be converted by the enzyme P450 aromatase (ARO) to estrone and 17β-estradiol (17β-E_2) respectively. This occurs also in astrocytes, which display ARO, but not in microglia (Garcia-Segura *et al.* 2003). In neurons, as well as in astrocytes, PROG and testosterone may be metabolized by the enzymatic complex formed by 5α-reductase (5α-R) and 3α-hydroxysteroid dehydrogenase (3α-HSD) into dihydroprogesterone (DHP) and tetrahydroprogesterone (THP), also known as allopregnanolone, or dihydrotestosterone (DHT) and 5α-androstane-3α,17β-diol (3α-Diol) respectively (Melcangi *et al.* 2008). Although these pathways are shared by microglia, this cell type is not able to produce PREG or PROG. Moreover, expressing 17β-HSD, they synthesize androstenediol from DHEA (Jellinck *et al.* 2007) and testosterone from

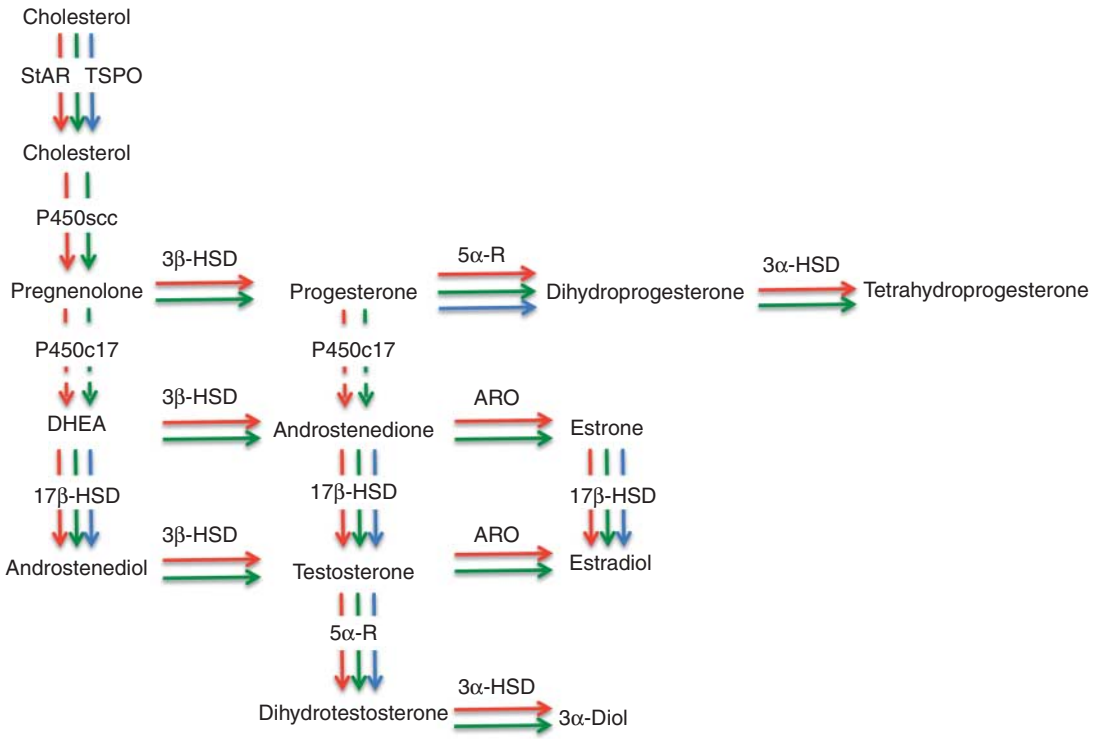

Figure 1 Schematic representation of neurosteroidogenesis. Arrows represent cellular localization in neurons (red), astrocytes (green), and microglia (blue).

androstenedione (Jellinck *et al.* 2006, 2007). Finally, since ARO is not expressed, microglial cells produce estradiol only from estrone and not from testosterone (Gottfried-Blackmore *et al.* 2008).

The metabolism of PROG and testosterone has a deep impact on the mechanism of action of these neuroactive steroids. Indeed, while DHP, like PROG, is able to interact with the classical steroid receptor, the PROG receptor (PR; Melcangi *et al.* 2008), THP is a potent ligand of a non-classical steroid receptor, such as the GABA-A receptor (Lambert *et al.* 2003, Belelli & Lambert 2005). Similarly, DHT is able to interact with the androgen receptor (AR) while 3α-diol is a ligand of the GABA-A receptor (Melcangi *et al.* 2008). Thus, metabolic conversion of PROG and testosterone into their derivatives might differently and specifically modulate the mechanism of action of the respective precursor molecules by recruiting CNS-specific pathways.

Both neurons and glial cells express classical steroid receptors (Melcangi *et al.* 2001, 2008, Brinton *et al.* 2008). However, not all glial cell types express the same repertoire of steroid receptors and their expression changes in relation to the activation state of cells, to the regional localization and the developmental stage. For instance, estrogen receptor α (ERα) is expressed in microglial cells, while ERβ, AR, and PR seem not to be under physiological conditions (Sierra *et al.* 2007, 2008). In male rats, AR-positive astrocytes were observed in the cerebral cortex, but only in postnatal day 10 animals (DonCarlos *et al.* 2006), while in the adult animals AR-positive astrocytes were observed in the arcuate nucleus and in the hippocampal formation (Tabori *et al.* 2005, DonCarlos *et al.* 2006).

Both steroid receptor expression and metabolism are modified by different insults. In rats, for example, brain injury induces the expression of ERα in vimentin or glial fibrillary acidic protein (GFAP)-positive astrocytes and of AR in Griffonia simplicifolia lectin-1 or MHC-II-positive microglia, suggesting that the expression of several receptors in different cell types is necessary for the correct modulation of the response to the insults (García-Ovejero *et al.* 2002).

Neuroinflammation: the main features

Neuroinflammation is a local CNS inflammatory reaction, which represents the coordinated cellular and molecular response to injurious stimuli, aimed at eliminating or neutralizing them and restoring tissue integrity (Fig. 2). The appropriate regulation of this process facilitates recovery, while uncontrolled neuroinflammation contributes to pathology.

Microglia and astrocytes are the two cell types resident within the CNS and mainly involved in the local organization of the neuroinflammatory response. Microglia are involved in regulatory processes critical for development, maintenance of neuronal environment, repair, and injury. In the normal, healthy brain, these cells are in a so-called 'resting state' characterized by low expression of membrane receptors that serve immunological functions (Hanisch & Kettenmann 2007). Although 'resting', microglia constantly monitor for changes in the surrounding environment and are ready to get activated to fight off any threats to tissue integrity. When stimulated, microglia acquire an ameboid morphology and present an upregulated catalog of surface molecules (Oehmichen & Gencic 1975, Cho *et al.* 2006), such as MHC, chemokine receptors, and CD14 (Rock *et al.* 2004). This activated state also coincides with the production of soluble mediators both detrimental, such as pro-inflammatory cytokines, reactive oxygen species, and reactive nitrogen species (Sawada *et al.* 1989, Moss & Bates 2001, Viviani *et al.* 2001, Liu *et al.* 2002, Tansey *et al.* 2007), and beneficial (i.e. anti-inflammatory cytokines and tropic factors) (Morgan *et al.* 2004, Liao *et al.* 2005, Muller *et al.* 2006; Fig. 2). A balanced production of those factors contributes to restore CNS function.

While microglial cells are generally considered as the main resident immune cells of the brain, it is important to note that astrocytes are immunocompetent cells as well, and they also act as important regulators of CNS inflammation. Astrocytes are the most abundant glial cells and are essential for brain homeostasis and neuronal functions (Benarroch 2005, Farina *et al.* 2007). Like microglia, astrocytes become activated – a process known 'astrogliosis', which is characterized by altered gene expression, increased expression of marker molecules (i.e. GFAP and vimentin), hypertrophy, and proliferation (Ridet *et al.* 1997). Activated astrocytes release as well a wide array of immune mediators such as cytokines, chemokines, and growth factors, contributing either to neuroprotective or neurotoxic effects (Farina *et al.* 2007) raised by microglia (Fig. 2).

The neuroinflammatory response is not only confined to glial cells. Peripheral immune cells also, and no less crucially, participate (Schwartz *et al.* 2006). In fact, the release of the above mediators by glial cells leads to the recruitment of macrophages, monocytes, and lymphocytes (T and B cells) that participate in sustaining the local response to an acute or chronic CNS insult (Schwartz *et al.* 2006). This easily occurs through the compromised blood–brain barrier (BBB), a feature accompanying several CNS diseases. T-cell invasion of the CNS determines the organization of an adaptive immune response whose quality will be defined by the characteristics of the invading lymphocytes. In fact, in response to inflammatory events, CD4+T helper (Th) cells can potentially differentiate

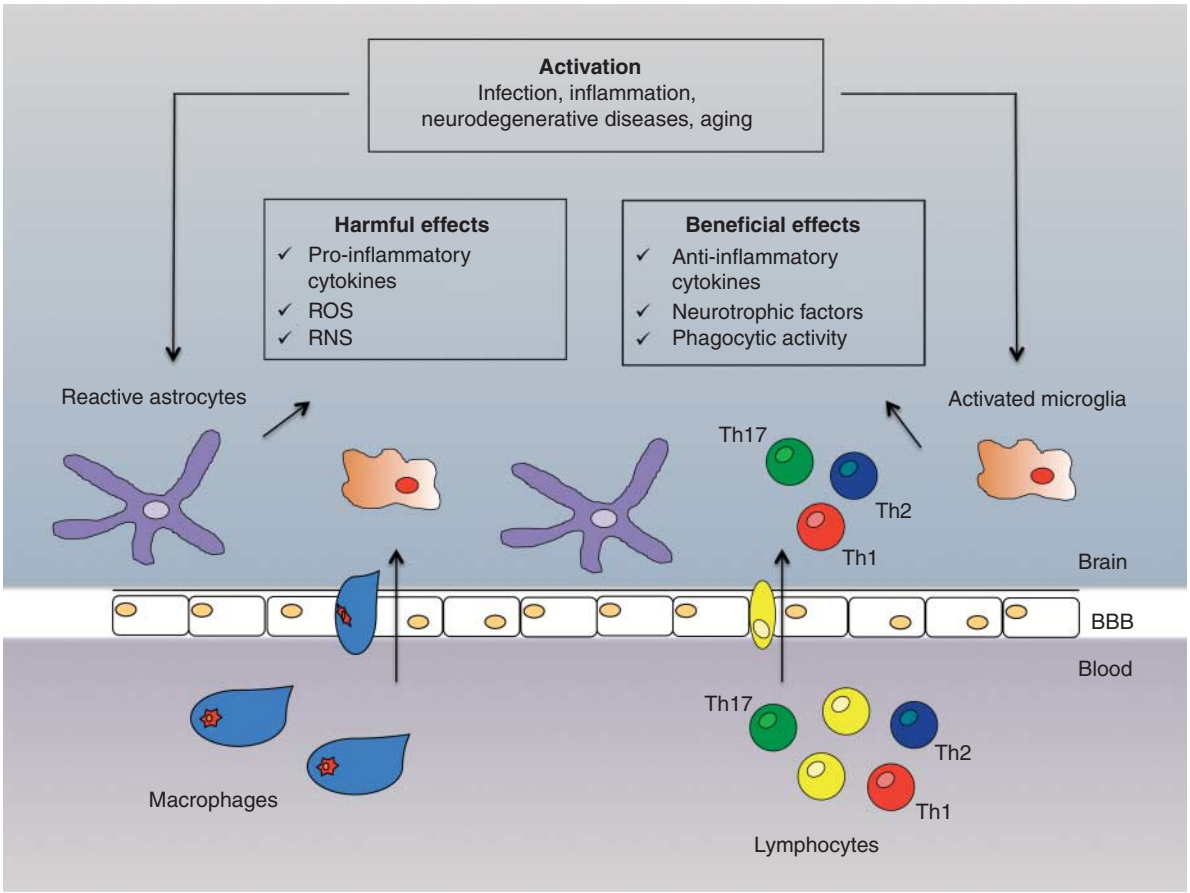

Figure 2 Inflammatory processes that occur in the CNS. Different events (inflammation, infection, aging, neurodegenerative diseases) could be the causative factor for the activation of microglia and astrocytes, the immune cells of CNS. It leads to a series of concomitant detrimental and beneficial effects. Harmful glial-mediated effects include the production of cytotoxic molecules (ROS, reactive oxygen species and RNS, reactive nitrogen species) and pro-inflammatory cytokines (IL1β, TNF-α, IL6). By contrast, glial cells also mediate positive and reparative effects, including the release of tropic factors and anti-inflammatory cytokines (IL10, TGF-β), and the clearance of cellular debris by phagocytosis. The neuroinflammation is often accompanied by the presence of peripheral immune cells (macrophages and lymphocytes) that cross the compromised BBB and sustain the inflammatory reactions in the CNS.

into Th1, Th2, and Th17 subsets depending on the cytokine milieu (Liew 2002). Th1 cells are largely considered to be pro-inflammatory in nature, aiding in the activation of macrophages and other immune cell subsets (Wee Yong 2010), while Th2 cells are considered regulatory/anti-inflammatory by virtue of the cytokines produced, which include interleukin (IL)4, IL5, IL10, and IL13 (Wee Yong 2010). A third arm of differentiation of the Th cell is to the pro-inflammatory Th17 subset characterized by the production of IL17 (Kebir *et al.* 2007). Finally another subclass is regulatory T cells (Tregs), involved in the control of immune homeostasis and self-tolerance (Mills 2004).

As it appears from the mediators produced and the cell types recruited, neuroinflammation is a two-edged sword. In most cases it constitutes a beneficial process for the CNS, since it tends to minimize the injury and contributes to the repair of damaged tissue (Czlonkowska & Kurkowska-Jastrzebska 2011). However, in some situations (Fig. 2), when the insults may persists and/or the inflammatory process may get out of control, the chronic activation of the immune response could be harmful. A shift from a homeostatic balance of inflammatory mediators toward a pro-inflammatory state has been observed not only in 'classical' pathological conditions but also in aging (Fig. 2; Viviani & Boraso 2011). In particular, the balance between pro- and anti-inflammatory cytokines is lost during aging, possibly contributing to an unsuccessful maintenance at the molecular, cellular, and tissue level leading to age-related dysfunction as well as to an enhanced brain vulnerability to diseases, pathogens, environmental factors, or stress.

Neuroactive steroids as neuroinflammatory modulators

It is well established that numerous pathologies show differences in etiology and progression according to sex. Autoimmune diseases, for example, and in particular, multiple sclerosis (MS), have a female preponderance (Hughes 2012). Also neurodegenerative diseases, like for instance Alzheimer's disease (AD) and Parkinson's disease (PD), show differences between the sexes in susceptibility and outcomes in response to therapies (Melcangi & Garcia-Segura 2010). Indeed, women seem to be more affected than men in AD and protected from PD, with a better response to levodopa treatment (Melcangi & Garcia-Segura 2010). Moreover, sex differences on response to treatment are also reported after brain injury, with women showing better cognitive performance than men after therapy (Melcangi & Garcia-Segura 2010).

The influence of the hormonal milieu on the etiopathogenesis of these conditions has been supported also by other observations done both in humans and animal models. Actually, changes in neuroactive steroid levels are evident in autopsy brain tissue from AD, PD, and MS patients (Naylor *et al.* 2010, Luchetti *et al.* 2011*a*,*b*, Noorbakhsh *et al.* 2011); similarly significant modifications happen also in the CNS of PD and experimental autoimmune encephalomyelitis (EAE) models as well as of brain or spinal trauma (Labombarda *et al.* 2006, Meffre *et al.* 2007, Caruso *et al.* 2010, Giatti *et al.* 2010, 2012, Melcangi *et al.* 2012). Moreover, the variation of hormonal levels in conditions such as castration, pregnancy, and the phase of estrous cycle may also influence the course of pathologies (Melcangi & Garcia-Segura 2010).

As mentioned above, neuroinflammation is an important feature of these pathologies. Therefore, also the effect of neuroactive steroids on neuroinflammatory pathways has been specifically analyzed. Several observations have been obtained *in vitro*, using cultures of microglia or astrocytes exposed to lipopolysaccharide (LPS). These findings have been recently reviewed (Arevalo *et al.* 2012), therefore, in this study, we focus our attention on *in vivo* observations obtained in experimental animal models. In particular, several observations have been obtained in MS animal models and following CNS injury. For instance, in EAE animals, estrogen treatment reduces the pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL6; chemokines and their receptors (e.g. CCL2, CCL3, CXCL2, CCR2, CCR3, and CXCR5), and increases anti-inflammatory transforming growth factor (TGF)-β2 and -3 (Spence & Voskuhl 2012). Moreover, their treatment suppresses Th1 (Bebo *et al.* 2001, Offner 2004) and Th17 cell (Wang *et al.* 2009) functions, promoting Treg cell regulation (Offner 2004). In the same animal model, other evidences report that PROG was able to reduce inflammatory markers (i.e. microglia activation, IL1β, IL2, and IL17) (Yates *et al.* 2010, Giatti *et al.* 2012).

In experimental models of injury, such as the traumatic brain injury (TBI) model, PROG treatment reduces edema, accumulation of astrocytes in the cortex, nuclear factor kappa B (NFkB) p65, active C3 fragments, IL1β, and TNF-α (Garcia-Estrada *et al.* 1993, Grossman *et al.* 2004, He *et al.* 2004, Pettus *et al.* 2005, Feeser & Loria 2011). Moreover, it attenuates the reaction of astrocytes and microglial/macrophage cells in spinal cord injury models (Garay *et al.* 2011, Labombarda *et al.* 2011) and decreases the lesion volume and the expression of IL1β, inducible nitric oxide synthase (iNOS; Gibson *et al.* 2008), ionized calcium-binding adapter molecule 1 (Iba1), and cyclooxygenase-2 in ischemic stroke models (Jiang *et al.* 2011). Also, testosterone treatment in TBI decreases vimentin, MHCII, and GFAP immunoreactive cells (Garcia-Estrada *et al.* 1993, Barreto *et al.* 2007) and after middle cerebral artery occlusion decreases GFAP immunostaining and astrocyte hypertrophy around the infarcted area (Pan *et al.* 2005). All these data underline the ability of neuroactive steroids to positively influence the inflammatory events in different neurodegenerative conditions by suppressing the pro-inflammatory and emphasizing the anti-inflammatory response.

Anti-inflammatory effects have been also reported after treatment with testosterone or PROG metabolites. Again, in the EAE model DHT reduces pro-inflammatory IFN-γ whereas it increases anti-inflammatory IL10 (Dalal *et al.* 1997), and THP treatment reduces the immunoreactivity of Iba1, the monocytoid cell marker, and CD3ε, a lymphocytic marker, in lumbar spinal cord (Noorbakhsh *et al.* 2011). In particular, THP diminishes phorbol ester myristate-induced expression of pro-inflammatory genes in primary monocyte-derived macrophage cultures, while it does not affect antigen-specific proliferation of CD4+T cells as well as the expression of IFN-γ and IL17 *in vitro* in the presence of myelin oligodendrocyte glycoprotein (Noorbakhsh *et al.* 2011). These results, together with the absence of monocytoid and lymphocytic markers in the spinal cord, suggest that THP specifically inhibits the activation of both macrophages and microglia as well as the penetration of circulating lymphocytes and macrophages toward the CNS, thus preventing the exacerbation of the immune response. Consistent with the role of a deregulated inflammatory response in the progression of CNS diseases, THP treatment diminishes EAE severity (Noorbakhsh *et al.* 2011). THP anti-inflammatory effect seems to apply also to CNS diseases different in nature from EAE. Indeed, in ischemic stroke, THP is able to reduce the infarct size,

production of pro-inflammatory cytokines like TNF-α and IL6, as well as to protect BBB disruption (Ishrat *et al.* 2010). Moreover, in the TBI model this neuroactive metabolite of PROG decreases the expression of IL1β, TNF-α (He *et al.* 2004) and increases CD55, a potent inhibitor of the complement convertases that are activators of the inflammatory cascade (VanLandingham *et al.* 2007). Although no direct evidence exists, GABA-A receptors have been evoked to explain part of the anti-inflammatory effect of THP. Proofs of concept are the observations that i) THP *per se* does not act through the classical intra-nuclear PR but in its action recruits GABA-A receptors (Lambert *et al.* 2003, Belelli & Lambert 2005), ii) this neurotransmitter receptor is also expressed on resident and circulating monocytoid cells of the immune system (Alam *et al.* 2006, Bhat *et al.* 2010) as well as on astrocyte and microglia (Lee *et al.* 2011), and iii) GABA suppresses the reactive response of glia to the inflammatory stimulants LPS and IFN-γ by inhibiting induction of inflammatory pathways mediated by NFkB and P38 MAP kinase (Lee *et al.* 2011). Nevertheless, as THP can be reversibly converted to DHP (Melcangi *et al.* 2008), the recruitment of the classical nuclear PR cannot be radically excluded.

As demonstrated by Barreto *et al.* (2007), the effect of testosterone in reducing reactive astroglia and microglia in the TBI model seems to be ascribed to the conversion of this neuroactive steroid into its metabolites, 17β-E_2 (i.e. by ARO activity) or DHT (i.e. by the enzyme 5α-R). Indeed, treatment with these metabolites may partially mimic the effect of testosterone (Barreto *et al.* 2007). Similar observations were obtained in the case of PROG. Indeed, after kainic acid injection, PROG as well as its metabolites (i.e. DHP and THP) reduces reactive gliosis (Ciriza *et al.* 2004). Inhibition of PROG-metabolizing enzymes (i.e. 5α-R and 3α-HSD) blocked the anti-gliotic effect of PROG (Ciriza *et al.* 2006). This is a very interesting finding in light of the observation that in experimental models reproducing different neurological diseases, the levels of neuroactive steroids and particularly the conversions of PROG and testosterone into their metabolites are affected (Labombarda *et al.* 2006, Meffre *et al.* 2007, Caruso *et al.* 2008, 2010, Giatti *et al.* 2010, Pesaresi *et al.* 2010*b*, Melcangi *et al.* 2012). On this basis, it is possible to hypothesize that treatment with metabolites might be more effective than treatment with the substrate molecule in regulating the neuroinflammatory response. Thus, exploring the potential anti-inflammatory effects of neuroactive steroid metabolites, together with their mechanism of action, in neurodegenerative events may provide important advances to a more effective therapeutic approach. This hypothesis is strengthened by recent *in vitro* observations, obtained with androstenediol (i.e. a metabolite of DHEA) showing that i) LPS decreases the expression of 17β-HSD (i.e. the enzyme converting DHEA into androstenediol) in microglia cultures and ii) androstenediol, through the interaction with ERβ, represses the transcription of pro-inflammatory mediators such as IL6, IL1β, and iNOS in microglia or astrocytes (Saijo *et al.* 2011). In line with these *in vitro* observations, *in vivo* treatment with androstenediol has been reported to be more potent than its precursor (i.e. DHEA) in blocking the ability of LPS to induce IL6 expression in the substantia nigra (Saijo *et al.* 2011).

Concluding remarks and perspectives

Neuroinflammation is a process that requires to be regulated because both deficient and excessive responses will result in pathological conditions. In particular, chronic inflammation is a long-standing and often self-perpetuating response that may negatively affect neuronal function and viability, thus contributing to disease progression. Understanding CNS immunity requires attention to the temporary relation between insult, inflammatory response, and control of pro- and anti-inflammatory processes. Like in a symphony, each of these aspects is necessary and instrumental for a harmonic composition that will be reached only under tight control of every single step. Based on the dual role of inflammation, a proper anti-inflammatory approach should not simply block the onset of the process. In doing so, the deleterious effects of inflammation will be inhibited, but at the same time the inflammatory pathways that lead to neuroprotection will not be preserved. A possible approach to control neuroinflammation could consist of the restoration of the feedback mechanisms that enable the brain to regulate

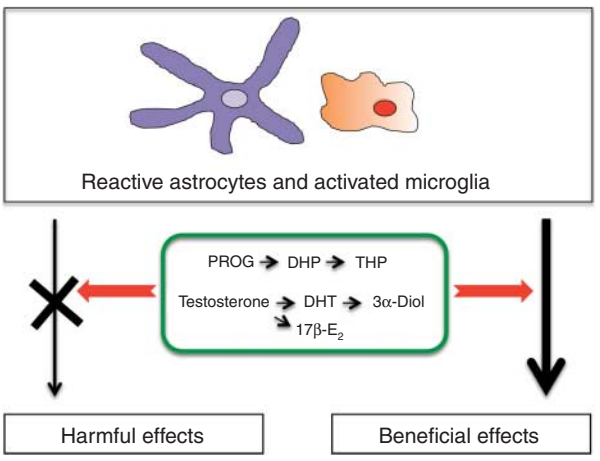

Figure 3 Progesterone and testosterone metabolites, reducing pro-inflammatory and promoting anti-inflammatory response of activated glial cells, may represent novel therapeutic approaches to reduce brain inflammation.

the process. This goal might be reached respecting the timing and local control of inflammation in order to boost the endogenous neuroprotective response directly or interfering with the mechanisms that blunt this response in conditions of injury. In this scenario, neuroactive steroids together with their metabolites provide several points for discussion and present several attractive features to be considered as effective and promising anti-inflammatory mediators. Neuroactive steroids have been proved to positively affect neuroinflammation, also by inhibiting the pro-inflammatory and reinforcing the anti-inflammatory response (Fig. 3). Their action is regulated by a dynamic system based on a differential expression and distribution of specific metabolic enzymes and receptors, both sensitive to pathological stages. In addition, neuroactive steroid metabolism, by providing a plethora of compounds characterized by different potency and mechanisms, might modulate diverse aspects of neuroinflammation. Although the observations so far obtained suggest a beneficial effect of neuroactive steroids, timing, location, metabolism, and molecular mechanisms recruited in modulating neuroinflammation remain to be still clarified. Deciphering the setting of the neuroactive steroid system along with the development of different stages of neuroinflammation and the cross-talk between these two processes will be instrumental for the development of novel approaches aimed at restoring a 'physiological' neuroinflammation.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

The financial support of Fondazione San Paolo (Progetto Neuroscienze PF-2009.1180) to R C M is gratefully acknowledged.

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Received in final form 5 September 2012
Accepted 10 September 2012
Made available online as an Accepted Preprint
10 September 2012