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The role of G protein-coupled estrogen receptor 1 on neurological disorders

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ABSTRACT

G protein-coupled estrogen receptor 1 (GPER) is a membrane-associated estrogen receptor (ER) associated with rapid estrogen-mediated effects. Over recent years GPER emerged has a potential therapeutic target to induce neuroprotection, avoiding the side effects elicited by the activation of classical ERs. The putative neuroprotection triggered by GPER selective activation was demonstrated in mood disorders, Alzheimer's disease or Parkinson's disease of male and female *in vivo* rodent models. In others, like ischemic stroke, the results are contradictory and currently there is no consensus on the role played by this receptor. However, it seems clear that sex is a biological variable that may impact the results. The major objective of this review is to provide an overview about the physiological effects of GPER in the brain and its putative contribution in neurodegenerative disorders, discussing the data about the signaling pathways involved, as well as, the diverse effects observed.

1. Introduction

Estradiol (E_2) is a form of estrogen that regulates multiple functions in human body (Brann et al., 2007). It controls ovulation and the development of female sex characteristics, being classically considered a reproductive hormone, due to its well-known role in feedback signaling in the hypothalamic-pituitary-ovarian axis (Brann et al., 2007; Kelly et al., 2005; Petersen et al., 2003).

Estrogens refer to any substance, natural or synthetic, that mimics the effects of the natural hormone (Liang and Shang, 2013). The three major naturally occurring forms of estrogens are estrone, E_2, and estriol, being E_2 the most potent and prevalent form, although several metabolites also have estrogenic hormonal activity (Liang and Shang, 2013). The actions of estrogens are mediated by estrogen receptors (ER) (Hewitt and Korach, 2003). ERα was first described in the 1960s (Soloff and Szego, 1969; Talwar et al., 1964), whereas ERβ was described almost 30 years later (Kuiper et al., 1996). These homologous receptors, described as ligand-activated nuclear transcription factors (Carroll and Brown, 2006), are predominately present in nucleus and cytoplasm, with less than 2% on cellular membrane (Edwards, 2005; Klinge, 2000). Each ER exhibits differential tissue expression patterns, but both regulate gene transcription through classical genomic pathways (Prossnitz and Barton, 2009, 2014; Schultz-Norton et al., 2011), or by modulating cellular signaling pathways such as the mitogen-activated protein kinases (MAPKs)/extracellular signal-regulated kinases (ERKs) (Wade et al., 2001), modulation of intracellular calcium (Brailoiu et al., 2007; Revankar et al., 2005; Roque et al., 2018), cyclic adenosine monophosphate (cAMP) production (Filardo et al., 2002; Thomas and Dong, 2006), and regulation of phosphatidylinositol 3-kinase (PI3Ks) (Revankar et al., 2005).

In the late 1990s, the G protein–coupled estrogen receptor 1 (GPER or GPR30) was identified as a novel estrogen receptor (Filardo et al.,

Abbreviations: MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP+, 1-methyl-4-phenylpyridinium; AD, Alzheimer's disease; ASD, autism spectrum disorder; EAE, autoimmune encephalomyelitis; BLA, basolateral amygdala; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; JNK, c-Jun N-terminal kinase; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; DAT, dopamine transporter; EGFR, epidermal growth factor receptor; E_2, estradiol; ER, estrogen receptors; ERK, extracellular signal-regulated kinases; ICI-182780, fulvestrant; GPER, G protein–coupled estrogen receptor 1; GDNF, glial cell-derived neurotrophic factor; iNOS, inducible nitric oxide synthase; IP3, inositol 1,4,5-trisphosphate; IFNγ, interferon γ; IS, ischemic stroke; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; MMP, matrix metalloproteinase; MCAO, middle cerebral artery occlusion; MAPKs, mitogen-activated protein kinases; MS, multiple sclerosis; NGF, nerve growth factor; NO, nitric oxide; OVX, ovariectomized; OGD, oxygen and glucose deprivation; PD, Parkinson's disease; PNS, peripheral nervous system; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-triphosphate; PLC, phospholipase C; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; SSRI, selective serotonin reuptake inhibitors; SK2, small conductance calcium-activated potassium channel 2; SCI, spinal cord injury; TNFα, tumor necrosis factor α; VEGF-A, vascular endothelial growth factor A; VMAT, vesicular monoamine transporter

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2000). It was described as an orphan receptor belonging to the family of 7-transmembrane spanning G protein-coupled receptors (Kvingedal and Smeland, 1997; Owman et al., 1996). In 2000, Filardo et al. demonstrated that E_2-mediated activation of ERK1/2 was dependent on the expression of this receptor, and named it GPR30 (Filardo et al., 2000). In 2005, Revankar et al. (Revankar et al., 2005) and Thomas and Dong (Thomas and Dong, 2006) described the binding of E_2 to GPR30, suggesting that GPR30 was an E_2-binding receptor, which led to its current designation as G protein-coupled estrogen receptor 1 in 2007 (Prossnitz and Barton, 2012). Since its identification, GPER has been described nearly in every system of the human body, including reproductive (Otto et al., 2009; Wang et al., 2008), cardiovascular (Patel et al., 2010; Recchia et al., 2011), endocrine (Hazell et al., 2009) and nervous system (Brailoiu et al., 2007; Hazell et al., 2009).

Estrogens mediate genomic effects through the classical ERs that are characterized by changes in gene transcription and occur in the time frame of hours to days (Prossnitz et al., 2008). Furthermore, it was also reported that estrogens mediate a variety of "rapid" cellular responses that occur in the time frame of seconds to minutes (Prossnitz et al., 2008), inconsistent with *de novo* transcription and protein synthesis (Falkenstein et al., 2000). These rapid estrogen-mediated effects have been associated with the activation of membrane-associated ERs, and are referred as "non-genomic" (Fu and Simoncini, 2008; Levin, 2009). The signaling pathways that triggers these rapid estrogen-mediated effects are diverse and can be induced by ERβ present near or at the plasma membrane (Mitterling et al., 2010), by the translocation of ERβ to the plasma membrane after E_2 treatment (Sheldahl et al., 2008), by the interaction of non-membrane ERα and ERβ with integral membrane proteins (Boulware et al., 2013; Boulware et al., 2005) or through the activation of GPER (Filardo et al., 2007; Filardo et al., 2000). In addition to the rapid GPER-mediated effects triggered by E_2 it was also described that GPER selective activation has also the ability to alter gene expression (Kanda and Watanabe, 2004). E_2, as well as a large number of other compounds that bind to classical ERs have also been demonstrated to bind to or activate GPER (Prossnitz and Barton, 2009). The discovery of GPER-selective ligands aided the research into the specific activities of GPER. Bologa et al. (2006), using a combination of virtual and biomolecular screening, identified the first selective GPER agonist, a non-steroidal compound named G1. The modulation of GPER was complemented with the identification of two selective antagonists, named G15 (Dennis et al., 2009) and G36 (Dennis et al., 2011). Binding studies about the affinity of these three selective ligands of GPER demonstrated that G1 has a binding affinity of about 11 nM (Bologa et al., 2006) compared to 3–6 nM for estrogen (Filardo et al., 2000). Whereas G15 and G36 presents a similar affinity of approximately 20 nM (Dennis et al., 2009; Dennis et al., 2011), but with G36 showing a decreased binding and activation of ERa compared to G15 (Dennis et al., 2011). Other compounds were described as having significant affinity to GPER, but in a non-selective manner, include 4-hydroxytamoxifen (the active metabolite of Tamoxifen) (Vivacqua et al., 2006), raloxifene (Petrie et al., 2013), ICI182780 (Filardo et al., 2000; Filardo et al., 2002; Revankar et al., 2005), Genistein (Thomas and Dong, 2006; Vivacqua et al., 2006) and Bisphenol A (Thomas and Dong, 2006). Since the identification of the GPER-selective ligands an increasing number of studies addressing the potential cellular and physiological effects of GPER selective activation in numerous systems including the central nervous system (CNS) were published.

The emerging notion that E_2 can act in multiple areas of the brain led to an increased focus on its effects on neuronal physiology and neuroplasticity (Srivastava et al., 2013). *In vitro* and *in vivo* studies indicated that E_2 is a potent physiological modulator of the CNS and participates in processes such as neurogenesis, regulation of neurotrophic factors expression and regulation of antioxidant mechanisms (Li et al., 2011; Ma et al., 2013; Suzuki et al., 2009). Estrogens were also associated with the regulation of cognitive processing (Davis et al., 2005; Hammond et al., 2009), memory (Fortress et al., 2013; Frick et al., 2015; Gabor et al., 2015; Kim et al., 2016; Kubota et al., 2016; Lymer et al., 2017; Zhao et al., 2010) and neurological disorders (Liu et al., 2009; Srivastava et al., 2013).

Selective activation of GPER by its agonist G1 enhances cognitive processes, such as learning and memory, in a manner similar to E_2 (Alexander et al., 2017). Besides, GPER is highly enriched in the brain and greatly expressed at the synapses, being involved in the rapid regulation of hippocampal dendritic morphology and synaptic plasticity (Alexander et al., 2017). G1 enhances recognition memory tasks (Gabor et al., 2015; Hawley et al., 2014; Kim et al., 2016; Kubota et al., 2016; Lymer et al., 2017; Wang et al., 2017), learning of specific tasks (Gibbs et al., 2014), and social recognition (Gabor et al., 2015; Lymer et al., 2017). In agreement with this, chronic treatment with the GPER selective antagonist G15 impairs acquisition of a spatial learning task (Hammond et al., 2012).

Over the recent years this receptor emerged has a potential therapeutic target to induce neuroprotection. This hypothesis was based on the ability of its selective agents to mimic the effects of E_2 without the feminizing or other adverse effects (Prossnitz and Barton, 2012). Activation of GPER may replicate the beneficial effects of E_2 in the brain avoiding the side effects associated with estrogen replacement therapies, like increased risk of coronary heart disease, breast cancer and stroke (Gibson et al., 2006; Pabon et al., 2014). In this review, we explore the expression pattern and signaling pathways of GPER, its role in the CNS, and relevance to neurological disorders.

2. Expression of GPER in the CNS

The expression of GPER is not restricted to traditionally estrogen responsive tissues (Prossnitz and Barton, 2012, 2014; Shi et al., 2013). Indeed, characterization of GPER using immunohistochemistry revealed a ubiquitous expression of this receptor in several tissues (Prossnitz and Barton, 2012, 2014; Shi et al., 2013). High levels of GPER expression are present in numerous organs, including male and female reproductive systems, heart, intestine, ovary, pancreatic islets, adipose tissue and inflammatory cells, and nervous system (Prossnitz and Barton, 2012, 2014; Shi et al., 2013).

On nervous system, GPER is similarly expressed throughout the CNS and peripheral nervous system (PNS) of male and female rodents (Brailoiu et al., 2007; Broughton et al., 2013; Dun et al., 2009; Hammond et al., 2011; Hazell et al., 2009; Matsuda et al., 2008). GPER immunoreactivity is observed in the forebrain (e.g. cortex, hypothalamus, hippocampus, hypothalamic-pituitary axis and striatum (Brailoiu et al., 2007; Broughton et al., 2013; Hammond et al., 2011; Hazell et al., 2009; Matsuda et al., 2008; Xu et al., 2009; Zhao et al., 2016), brainstem (e.g. the pontine nuclei locus coeruleus, brainstem autonomic nuclei (Brailoiu et al., 2007), cerebellum Purkinje layer (Hazell et al., 2009), spinal cord and autonomic and sensory ganglia (Dun et al., 2009). In addition, GPER is present in brain vasculature (Ding et al., 2009; Isensee et al., 2009). The levels of GPER expression are heterogeneous with GPER presenting high expression in hypothalamic-pituitary axis (Brailoiu et al., 2007), hippocampus (Brailoiu et al., 2007; Hammond et al., 2011; Matsuda et al., 2008), cortex (Hammond et al., 2011) and thalamus (Broughton et al., 2013). The hippocampus and frontal cortex present higher GPER mRNA levels than the septum and striatum (Hammond et al., 2011).

At a cellular level, GPER is expressed by neurons of different regions, such as the pyramidal neurons of the frontal cortex (Hammond et al., 2011), cholinergic neurons in the medial septum, striatum, diagonal band of Broca and nucleus basalis magnocellularis (Hammond et al., 2011), CA1-3 hippocampal neurons (Akama et al., 2013; Matsuda et al., 2008), GABAergic neurons in the dorsal striatum (Almey et al., 2016), dopaminergic neurons from ventral mesencephalon (Bessa et al., 2015). GPER expression was also reported in neurons from paraventricular nucleus (Xu et al., 2009), luteinizing hormone-releasing neurons (Noel et al., 2009), neurons of the dorsal and ventral horn of

the spinal cord as well as in sensory and autonomic neurons (Chen et al., 2015; Dun et al., 2009). Concerning glial cells, GPER is expressed by cortical and midbrain astrocytes (Bessa et al., 2015), by microglial cells from forebrain (Zhao et al., 2016) and ventral midbrain (Mendes-Oliveira et al., 2017) and by oligodendrocytes of spinal cord, corpus callosum and cortex (Hirahara et al., 2013). On brain vasculature, GPER is particularly expressed in the endothelial cell subpopulation of small arterial vessels (Isensee et al., 2009), and in smooth muscle cells (Ding et al., 2009; Isensee et al., 2009) and pericytes (Isensee et al., 2009).

At a sub-cellular level, GPER is expressed in the plasma membrane of neurons (Akama et al., 2013; Filardo et al., 2000; Funakoshi et al., 2006; Hammond et al., 2011; Thomas et al., 2005) and glial cells (Almey et al., 2012). GPER is also present in the cytoplasm, particularly in the membrane of intracellular compartments such as the endoplasmic reticulum (Matsuda et al., 2008; Otto et al., 2008; Revankar et al., 2005) and Golgi apparatus (Matsuda et al., 2008).

2.1. Sex differences in GPER expression

The expression pattern of GPER mRNA in human brain tissues (Feng and Gregor, 1997; O'Dowd et al., 1998; Owman et al., 1996) is similar to the receptor distribution profile observed in the rat brain, with no differences between sexes (Brailoiu et al., 2007). In contrast, in the zebra fish brain there is a higher expression in males than in females (Acharya and Veney, 2012). A clear sexually dimorphic distribution of GPER occurs in some areas of the hamster brain, with higher levels of GPER in the female hypothalamus and amygdala, and moderate and low levels in the male amygdala and hypothalamus, respectively (Canonaco et al., 2008).

Interestingly, some pathologies are associated with alterations in the pattern of distribution and expression of the GPER. This is the case of transient focal ischemia, where GPER distribution and expression increases in the brain of male mice, but not of intact or ovariectomized (OVX) females (Broughton et al., 2013).

2.2. Regulation of cell proliferation and differentiation by GPER

GPER have also been implicated in the modulation of hippocampal synaptic plasticity (Briz et al., 2015; Tian et al., 2013; Xu et al., 2018). Although these effects have not yet been demonstrated in pathological models, it was shown that Brain-derived neurotrophic factor (BDNF) expression triggered by GPER selective activation promotes synaptic plasticity (Briz et al., 2015; Xu et al., 2018), being these effect associated to the enhancement of spatial memory (Xu et al., 2018). GPER activation is also involved in the modulation of neuritogenesis induced by E_2 in primary hippocampal neurons (Ruiz-Palmero et al., 2013).

Furthermore, it is known that E_2 plays an important trophic and protective role in the adult brain, being essential to the maintenance of normal brain functions, and to protect the brain against neural injuries through different mechanisms, including the stimulation of neurogenesis. The first evidence of the modulating effect of estrogens on neurogenesis was achieved when scientists noticed that, in the reproductive cycle of mammals, higher estrogen levels were accompanied by increased cell proliferation in the dentate gyrus of the hippocampus and, contrariwise, a reduction of circulating estrogens resulted in a significant decrease in the proliferation of hippocampal precursors (Tanapat et al., 1999).

To investigate the effect of GPER on estrogens action in modulating neural cell proliferation and differentiation, Okada et al. (2010) used E_2 conjugated with bovine serum albumin, impeding E_2 to permeate the cell membrane. In this way, they showed that GPER is not directly involved in neural cell proliferation induced by estrogens, but it stimulates oligodendroglial differentiation from neural stem/precursor cells of the telencephalon of 15-day-old rat embryos (Okada et al., 2010). The same authors reported a couple of years before that administration of E_2 or bisphenol A, a xenoestrogen that activates GPER, stimulated the proliferation of neural stem/precursor cells in the absence of mitogens as well as the generation of oligodendrocytes (Okada et al., 2008).

In intact and OVX adult female rats treatment with E_2 or raloxifene, but not with tamoxifen, increased neurogenesis in the ipsilateral subventricular zone following transient middle-cerebral artery occlusion (Khan et al., 2015). Analysis of the role of GPER in hippocampal cell proliferation in adult female rats showed that treatment with GPER agonist decreased cell proliferation in adult OVX female rats, indicating a GPER-independent role of E_2 in hippocampal neurogenesis or, alternatively, an antagonistic effect of intracellular and membrane bound ER activation to maintain the levels of neurogenesis. GPER did not co-localize with progenitor cells in the subgranular zone of the dentate gyrus, indicating that the effects of GPER activation on neurogenesis may be indirect (Duarte-Guterman et al., 2015). In summary, the scarce information available suggests differential effects of GPER in the two neurogenic niches, with a neurogenesis promoting action of the receptor restricted to the subventricular area. The existing data also suggest that these effects may be sex-dependent.

2.3. GPER and aging

Little is known regarding the effect that aging may have on GPER functions. In OVX female rhesus monkeys it was demonstrated that the expression of GPER in gonadotrophin-releasing hormone neurons is not affected by age (Naugle and Gore, 2014). However, in hypothalamic regions of aged OVX females there were more cells expressing GPER and the expression of the GPER/cell was higher than in young OVX females (Naugle and Gore, 2014). In contrast, recent findings demonstrated that hippocampal GPER mRNA levels are decreased in aged OVX female mice when compared to young adult (Wu et al., 2018). Moreover, Wu et al. (2018) associated the reduction of GPER expression to the deprivation of E_2, since it was demonstrated that low levels of E_2 are associated with lower levels of GPER mRNA (Wu et al., 2018). Extrapolating to what happens in aging these data suggest that as the levels of E_2 begin to decrease there is a reduction in the expression of the GPER in females. On males, Xu et al. (2018) obtained similar results once hippocampal GPER expression is decreased in aged male mice compared to young adults (Xu et al., 2018). In males this reduction does not appear to compromise the effects mediated by GPER, since G1 was capable to enhance memory in aged mice (Xu et al., 2018). However, in OVX females the results indicate that the beneficial effects induced by GPER selective activation could be related to the critical period hypothesis. G1 exerted a neuroprotective effect after short-term E_2 deprivation, whereas after long-term E_2 deprivation neuroprotection was not achieved (Wu et al., 2018). Wu et al. (2018) also shows that GPER expression and function can be maintain with estrogens treatment during aging. E_2 treatment 10 weeks after ovariectomy prevents the reduction of GPER mRNA levels and triggers robust neuroprotective effects on aged females (Wu et al., 2018). The results also demonstrate that G15 attenuated the neuroprotective effects of E_2 within the CA1 region of the hippocampus when administered near the end of E_2 treatment (Wu et al., 2018), indicating that GPER may be an important factor in E_2 neuroprotection loss (Wu et al., 2018).

The data available indicates that during aging the expression of GPER seems to decrease in both sexes (Wu et al., 2018; Xu et al., 2018) and the expression pattern can be distinctly affected in different brain regions of OVX female (Naugle and Gore, 2014). Although GPER neuroprotective effects during aging can be maintained in males, on OVX females seems to be more complex. Considering that most of neurological diseases are age-related, it is crucial to develop further research to clarify if aging compromises the protective effects mediated by this receptor.

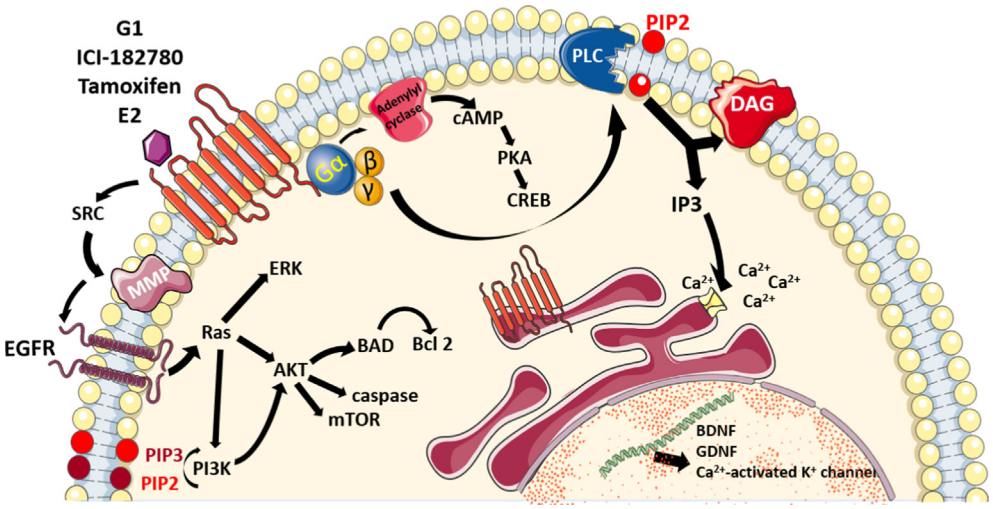

Fig. 1. Schematic representation of the diversity of signaling pathways regulated by GPER. Multiple agonists activate GPER: E2, selective estrogen receptor degraders (SERDs) such as Fulvestrant (ICI-182780), selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene, and selective agonists such as G1. GPER activation stimulates multiple cellular pathways, part of them mediated by transactivation of EGFR. *Abbreviations*: brain-derived neurotrophic factor (BDNF); cell-derived neurotrophic factor (GDNF); cyclic adenosine monophosphate (cAMP); diacylglycerol (DAG); epidermal growth factor receptor (EGFR); estradiol (E2); Estrogen receptors (ER); extracellular signal-regulated kinases (ERK); G protein–coupled estrogen receptor 1 (GPER); inositol 1,4,5-trisphosphate (IP3); mammalian target of rapamycin (mTOR); matrix metalloproteinase (MMP); phosphatidylinositol 3-kinase (PI3K); phosphatidylinositol 4,5-bisphosphate (PIP2); phosphatidylinositol-3,4,5-triphosphate (PIP3); phospholipase C (PLC); selective estrogen receptor degrader (SERD); selective estrogen receptor modulator (SERM);

3. Signaling pathways triggered by GPER activation

The signaling transduction mechanisms triggered by activation of GPER have been studied in various cell types and a large diversity of pathways have been proposed (Fig. 1) (Feldman and Limbird, 2017). Besides the mechanisms elicited by the independent activation of GPER, the interactions of GPER with EGFR (epidermal growth factor receptor), and also with the classic ERα and ERβ, have been reported (Filardo and Thomas, 2012; Prossnitz and Barton, 2012). The crosstalk between GPER and ERα/ERβ involves multiple forms of interactions: cooperative, antagonistic and dependent (Hadjimarkou and Vasudevan, 2018). GPER was initially considered to signal via Gαs, leading to activation of adenylyl cyclase and the consequent increase in cAMP levels and PKA activation (Filardo et al., 2007; Filardo et al., 2002; Thomas et al., 2005). However, it is known that GPER activation may also lead to inhibition of PKA through Gαi and Gαo (Ding et al., 2009), and these pathways coexist with other rapid signaling pathways such as the activation of ERK pathway (Filardo et al., 2002), the activation of kinases such as PI3K (Petrie et al., 2013; Revankar et al., 2005) or PKC (Goswami et al., 2011), intracellular calcium mobilization (Filardo et al., 2007; Revankar et al., 2005; Revankar et al., 2007; Tica et al., 2011), or activation of ion channels (Fraser et al., 2010). Besides triggering rapid signaling events, GPER activation leads to upregulation of nerve growth factor (NGF) via c-fos expression (Kanda and Watanabe, 2003), cyclin D2 and Bcl-2 (Kanda and Watanabe, 2004).

Concerning neuronal cells/tissues, activation of the cell survival PI3K/Akt pathway was associated with the protection mediated by GPER activation in models of Alzheimer's disease (AD) (Wang et al., 2017), Parkinson's disease (PD) (Bessa et al., 2015), spinal cord injury (SCI) (Chen et al., 2015), and traumatic brain injury (Wang et al., 2017). Moreover, activation of PI3K signaling by GPER participates in the control of neuritogenesis in developing hippocampal neurons (Ruiz-Palmero et al., 2013) and on the protection of cognitive function (Wang et al., 2017). Survival promoted by GPER activation was also associated with the regulation of the c-Jun N-terminal kinase (JNK) pathway. In a rat model of global cerebral ischemia G1 exerts significant neuroprotection through the rapid activation of the pro-survival kinases, Akt and ERK, while decreasing pro-apoptotic effects of JNK activation (Tang et al., 2014). In addition to regulating cell survival, control of the JNK pathway by GPER also regulates memory since GPER activation in the dorsal hippocampus enhances hippocampal memory in a JNK-dependent manner and independently from ERα and ERβ (Kim et al., 2016), furthermore it was also demonstrated that JNK signaling is triggered via GPER activation during object-in-place learning, and possibly is E_2-independent (Mitchnick et al., 2019).

The phospholipase C (PLC) pathway is also a target of GPER. Our group showed recently that in rat cortical astrocytes, but not in neurons, GPER activation is able to regulate the PLC pathway. Moreover, activation of this pathway promotes the increase in intracellular Ca^{2+} levels and induces the apoptosis of astrocytes (Roque et al., 2018). In mesencephalic neuron-glia cultures protection induced by G1 against the dopaminergic toxin 1-methyl-4-phenylpyridinium (MPP^+) was associated with the involvement of three different pathways: MAPK, PI3K and PLC pathways (Bessa et al., 2015).

Together, the existing data show that GPER has the ability to regulate a wide variety of signaling pathways, which vary between tissues and even between cells of a given tissue.

4. GPER and neurological disorders

Over the past decades, it was demonstrated that E_2 has an active role in diseases of the nervous system. Although these effects were initially associated with classical ERs, the identification of GPER and the evidence that GPER mRNA and protein were expressed throughout the CNS and PNS of rodents was accompanied by findings showing that GPER significantly contributes to E_2-mediated neurological benefits (Fig. 2) (Brailoiu et al., 2007; Dun et al., 2009; Hazell et al., 2009). The protection mediated by GPER selective activation involves a plethora of mechanisms as diverse as inhibition of pathways mediating apoptosis, stimulation of neurotrophic factors expression, modulation of ion channels, inhibition of neuroinflammatory processes, control of gliosis, maintenance of blood-brain barrier (BBB) and vascular function. These mechanisms are summarized in Table 1.

4.1. Ischemic Stroke (IS)

The role of GPER in cerebral ischemia has been studied since the identification of GPER selective ligands and the characterization of its expression in the CNS. The potential benefits of GPER modulation was assessed in *in vivo* and *in vitro* studies with conflicting results associated mostly with the amount of circulating estrogens or with the sex (Table 2).

Initial *in vivo* studies showed that G1 treatment replicates the effects of E_2 in promoting neuronal survival following global cerebral ischemia (Lebesgue et al., 2010; Prossnitz and Barton, 2012). These effects were demonstrated in OVX female rats (Lebesgue et al., 2010; Tang et al.,

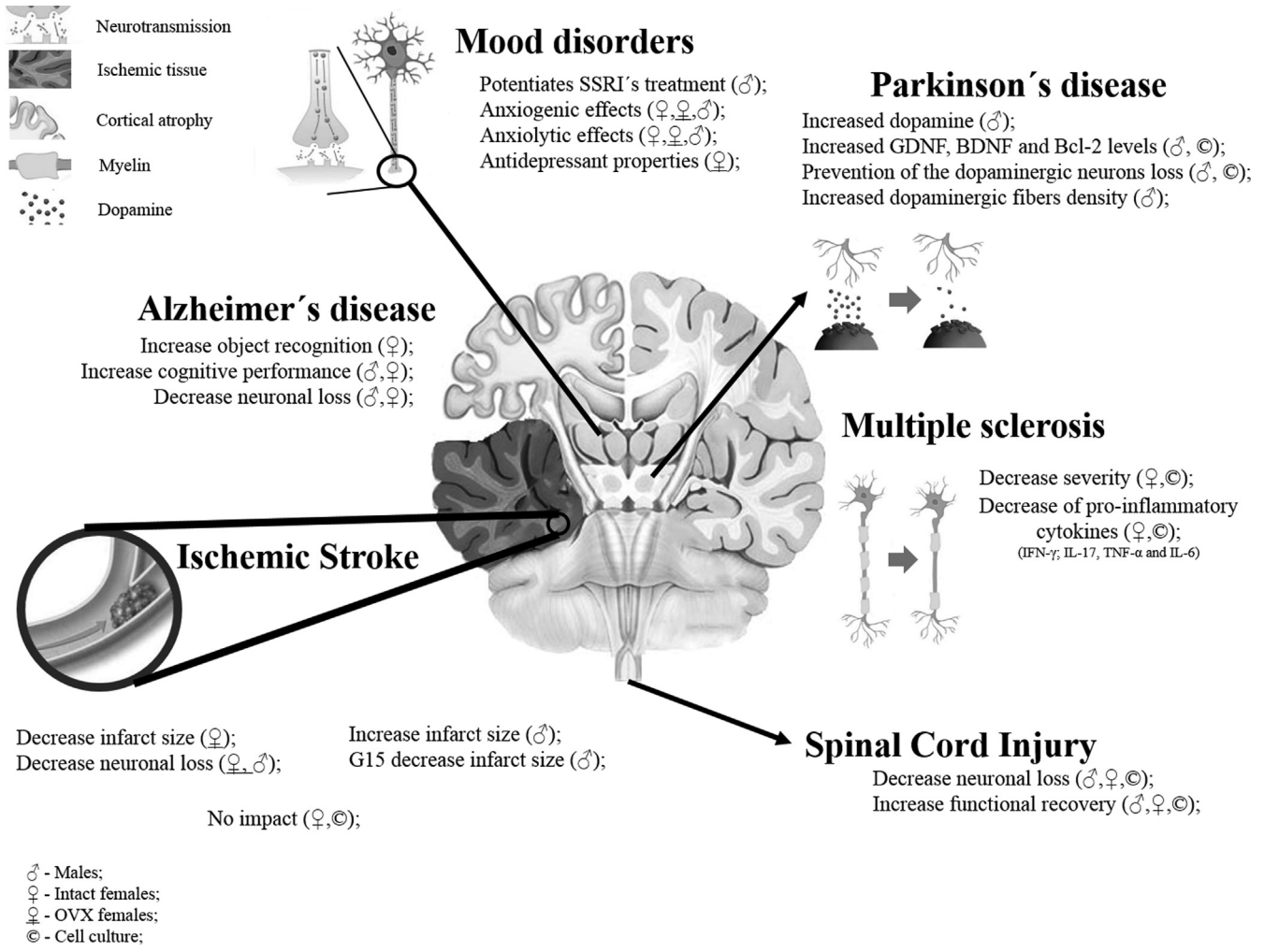

Fig. 2. Effects induced by GPER selective activation on brain disorders. *Abbreviations:* Brain-derived neurotrophic factor (BDNF); Glial cell-derived neurotrophic factor (GDNF); Selective serotonin reuptake inhibitors (SSRI).

2014) and mice (Zhang et al., 2010). It was demonstrated that GPER selective activation protected hippocampal CA1 pyramidal neurons exposed to ischemia (Lebesgue et al., 2010; Tang et al., 2014). Lebesgue et al. (2010) evaluated the effects induced by G1 on young (2 months) and middle aged (9–11 months) Sprague Dawley OVX female rats subjected to transient global cerebral ischemia and (Lebesgue et al., 2010). Immunohistochemical analysis indicated that G1 prevented hippocampal CA1 pyramidal neuronal loss triggered by ischemia (Lebesgue et al., 2010). It was also demonstrated that those effects were similar in young and middle aged animals (Lebesgue et al., 2010). The beneficial effects of GPER selective activation in OXV females were also described in mice. After middle cerebral artery occlusion (MCAO) exposure to G1 reduced the infarct volume (Zhang et al., 2010). Similar effects were reported by Broughton et al. (2014). Exposure to G1 reduced neurological deficit, apoptosis, and infarct volume in OVX female mice, but had no significant effect in intact females (Broughton et al., 2014). Broughton et al. (2014) also hypothesizes that in intact females the effects of GPER selective activation are not observed due to the amount of circulation estrogens (Broughton et al., 2014). These findings highlight the complex nature of endogenous estrogen signaling and raises the hypothesis that after an IS the effects induced by GPER selective activation could be affected by the amount of circulating estrogens.

The work from Broughton et al. (2014) also raises the hypothesis that the effects of GPER selective activation after ischemia might be related with the sex (Broughton et al., 2014). Since in young and aged males G1 unexpectedly and markedly exacerbates post-stroke neurological deficit and infarct volume, being those effects abrogated by G15 (Broughton et al., 2014). Which reinforce the body of evidence indicating that effects of estrogens in the female and male brain are not identical (Broughton et al., 2014). Contrary to the data obtained in males, there are evidences that after global cerebral ischemia exposure to G1 leads to a reduction of neuronal injury in hippocampal CA1 region and striatum (Kosaka et al., 2012). This neuroprotection is similar to the protection induced by E_2 treatment (Kosaka et al., 2012), which increases the controversy around GPER activation after cerebral ischemia.

The signaling pathways involved in the neuroprotective role of GPER upon an ischemic insult are not completely understood, *in vivo* studies demonstrated that in OVX females neuroprotection is associated to the rapid activation of the pro-survival kinases, Akt and ERK, while decreasing pro-apototic JNK activation (Tang et al., 2014). On males these neuroprotection in hippocampal and striatal neurons is associated to the up-regulation of protective ion channels, such as the small conductance calcium-activated potassium channel 2 (SK2) (Kosaka et al., 2012). On the other hand, the detrimental effects induced by G1 in males are associated to the increase in the expression of cleaved caspase-3 in peri-infarct neurons (Broughton et al., 2014).

On *in vitro* studies there are also some controversy, since it was demonstrated that selective activation of GPER with G1 does not induce any protection against an ischemic insult (Lamprecht and Morrison, 2014). In this study organotypic hippocampal slice cultures were

Table 1
Protective actions triggered by GPER activation in the brain.

Protective actions triggered by GPER (Mechanisms/Pathways)		References
Up-regulation of neurotrophic factors	BDNF	Bourque et al. (2014)
		Bourque et al. (2014)
	GDNF	Bessa et al. (2015)
		Cheng et al. (2017)
Up-regulation of anti-apoptotic proteins	Bcl-2	Bourque et al. (2014)
		Bourque et al. (2015)
Up-regulation of pro-survival kinases	Akt and ERK	Bourque et al. (2014)
		Tang et al. (2014)
	PI3K/Akt	Wang et al. (2017)
Up-regulation of protective ion channels	SK2	Kosaka et al. (2012)
Up-regulation of remyelination	Remyelination	Hirahara et al. (2013)
Down-regulation of pro-apoptotic kinases	JNK	Tang et al. (2014)
Modulation of synaptic plasticity	GABAergic and glutamatergic transmission	Tian et al. (2013)
	BDNF	Briz et al. (2015)
		Xu et al. (2018)
	Neuritogenesis	Ruiz-Palmero et al. (2013)
		Ruiz-Palmero et al. (2011)
Modulation of inflammation	IFNγ and IL-17	Blasko et al. (2009)
	IL-10	Yates et al. (2010)
	Astrogliosis	Day et al. (2013)
	IL-1β and TNFα	Zhao et al. 2016
	IL-1β, TNFα and IL-6	Guan et al. (2017)
	Phagocytic activity, iNOS expression and NO release	Mendes-Oliveira et al. (2017)
Restoration of vascular function	Arteriolar dilation	Murata et al. (2013)
Restoration of the BBB	Regulation of tight junctions and BBB permeability	Lu et al. (2016)
Increase of cell proliferation	Neural stem/precursor cells oligodendrocytes	Okada et al. (2008)
Cell differentiation	oligodendroglial	Okada et al. (2010)
Increase of neurogenesis		Khan et al. (2015)

Table 2
Effects induced by GPER selective activation in brain ischemia.

Major conclusions	Models	Reference
Selective GPER activation increases the number of hippocampal CA1 pyramidal neurons;	Sprague Dawley (OVX females); 4 vessel occlusion (10 min); Exposure to G1;	Lebesgue et al. (2010)
G1 replacement decreased infarct volume size;	C57Bl/6J mice (OVX females); MCAO (90 min); Exposure to G1;	Zhang et al. (2010)
Selective GPER activation reduces neuronal injury in the hippocampal CA1 region and striatum following global cerebral ischemia;	C57Bl/6J mice (males); Cardiac arrest and cardiopulmonary resuscitation (8 min); Exposure to G1;	Kosaka et al. (2012)
Ischemia increases GPER distribution and expression in the peri-infarct brain regions of male mice, but not in intact females or OVX mice;	C57Bl/6J mice (males, intact and OVX females); MCAO (30 min); GPER distribution;	Broughton et al. (2013)
Selective GPER activation restores vessel function of arterioles after hypoxia/reperfusion;	Male and female rats; Hypoxia (1 h) and reoxygenation injury; Exposure to G1;	Murata et al. (2013)
G1 worsened functional outcomes and increased post-stroke infarct volume size in males, effects that were blocked by G15; G15 improved functional outcomes and reduced infarct volume size after stroke in males; G1 reduced neurological deficit, apoptosis, and infarct volume in OVX females, but had no significant effect in intact females;	C57Bl/6J mice (males, intact female and OVX females); MCAO (30, 60 and 90 min); Exposure to G1 and G15;	Broughton et al. (2014)
Selective GPER activation does not induce any protection against an ischemic insult;	Organotypic hippocampal slice cultures prepared from Sprague Dawley rat pups; OGD (30 min); Exposure to G1;	Lamprecht and Morrison (2014)
G1 exerts significant neuroprotection against ischemia through the rapid enhanced activation of the pro-survival kinases, Akt and ERK, while decreasing pro-apoptotic JNK activation;	Sprague Dawley rats (OVX females); GCI (10 min); Intracerebroventricular administration of G1;	Tang, et al. (2014)
Ischemia increases GPER expression in the motor cortex and hippocampal region; GPER expressed in microglia mediated the anti-inflammatory effect of estradiol after ischemic stroke;	Sprague Dawley rats (intact females); 4 vessel occlusion (15 min); Exposure to G1 and G15;	Zhao et al. (2016)
Selective GPER activation after stroke ameliorates BBB permeability after global cerebral ischemia in OVX rats;	Sprague Dawley rats (OVX females); 4-vessel occlusion (20 min); Intracerebroventricular administration of G1;	Lu et al. (2016)

prepared from Sprague Dawley rat pups and exposed to 30 min of oxygen and glucose deprivation (OGD). After OGD the cultures were exposed to G1 during a reperfusion period of 24 h. The results demonstrated that G1 does not protect neurons from ischemic death nor increase the phosphorylation of Akt and/or ERK, unlike E_2 (Lamprecht and Morrison, 2014). More, the beneficial effects induced by E_2 after ischemia were maintained after GPER blockade by G15, thus suggesting that, in this case GPER is not involved in E_2-induced neuroprotection (Lamprecht and Morrison, 2014). Interestingly, in primary neuron-glia cortical cultures exposed to 4 h of OGD, GPER selective activation after ischemia does not induce any effect on neurons, but selectively promotes astrocytes death due to the rise of intracellular calcium levels via PLC (Roque et al., 2018). These results also show that GPER is coupled to different signaling pathways in neurons and astrocytes (Roque et al., 2018).

GPER might have an important role in the management of inflammation after an ischemic insult. Using adult female Sprague Dawley rats subjected to a global cerebral ischemia by four vessel occlusion and primary microglial cultures from neonatal rats Zhao et al. demonstrated that the GPER expressed in microglial cells directly mediates the anti-inflammatory effect of E_2 after an ischemic stroke (Zhao et al., 2016). G1 reduces IL-1β and Tumor necrosis factor α (TNFα) levels. Moreover, the specific GPER antagonist G15 was able to abolish the anti-inflammatory effect of E_2 (Zhao et al., 2016).

Another interesting effect induced by G1 after hypoxia/reperfusion is the ability to restore vessel function of arterioles, which points to the protection of the cerebrovasculature against an ischemic insult (Murata et al., 2013). In this study, rat cerebral penetrating arterioles from both sexes were isolated, cannulated and pressurized. To induce hypoxia, pial sheaths where incubated for 1 h in the hypoxic bath ($PO_2 < 2\%$), then transferred to the normoxic bath ($PO_2 = 21\%$) to induce reoxygenation and finally exposed to G1. The results indicate that G1 produces a vasodilatory response, which was partially dependent on endothelium derived Nitric oxide (NO), but not on arachidonic acid cascades and endothelial hyperpolarization factor. Additionally, G1 treatment after hypoxia/reperfusion injury fully restored endothelium-dependent dilation to ATP (Murata et al., 2013).

It was also described that GPER activation after stroke can attenuate the BBB disruption and vasogenic edema in early stage of ischemic stroke in OVX female rats (Lu et al., 2016). Bilateral intracerebroventricular administration of G1 to female Sprague-Dawley rats subjected to global cerebral ischemia significantly decreased immunoglobulin G extravasation and increased the tight junctions occludin and claudin-5 in the hippocampal CA1 region. Furthermore, G1 significantly decreased the protein levels of vascular endothelial growth factor A (VEGF-A) in the ischemic hippocampal CA1 region, which suggests that after ischemic injury GPER activation reduces tight junctions disruption via inhibition of VEGF-A expression (Lu et al., 2016).

Another controversial issue in relation to GPER is its expression pattern after an ischemic insult. In adult female Sprague Dawley rats subjected to global ischemia by four vessel occlusion there was a significant increase of GPER expression in the motor cortex and hippocampal region as demonstrated through immunohistochemical and western blot analysis (Zhao et al., 2016). Using the same techniques, Broughton et al. also reported a significant increase in GPER expression after an ischemic insult in hippocampus, somatosensory cortex and hypothalamus of males with no significant changes in intact or OVX females, which suggests a sex-dependent effect of ischemia on GPER expression (Broughton et al., 2013). The same study reported that GPER immunoreactive neurons in the peri-infarct regions appear more intensely labeled (Broughton et al., 2013).

The controversy around GPER expression after an ischemic insult could result, in part, by the use of different stroke models and periods of ischemia. The later directly influence the extension of the lesion and, consequently, the results. The discrepancies observed between *in vivo* and *in vitro* models may arise from the lack of some components in *in vitro* models that can influence GPER expression after stroke, such as the vascular or the immune cells.

4.2. GPER in neurodegenerative disorders

4.2.1. Alzheimer's disease

AD comprises a wide spectrum of alterations, which includes memory loss, functional decline, behavioral disturbances and dementia (Neugroschl and Wang, 2011). The hypothesis that GPER could be an effective therapy for reducing cognitive decline associated with aging and AD related dementia emerged from data showing that the GPER has the ability to modulate and enhance cognitive processes such as memory and learning (Gibbs et al., 2014; Hammond and Gibbs, 2011; Hammond et al., 2011; Hawley et al., 2014; Kim et al., 2016), known to be impaired in aging and AD (Hammond et al., 2011).

In the 5XFAD AD mouse model selective activation of GPER with G1 ameliorates memory impairment in the novel object recognition test in female, but not in male mice (Kubota et al., 2016). In females these effects are similar to the neuroprotection mediated by E_2. However, in males, despite the inconsistence in the effects observed, the bulk of evidence demonstrates a beneficial effect of E_2 on memory both in intact and gonadectomized male rodents (Frick et al., 2015).

4.2.2. Parkinson's disease

PD is a neurodegenerative disease characterized by the progressive and selective damage of the dopaminergic neurons from the nigrostriatal pathway. This damage results in a decrease of dopamine in the striatum, which leads to several motor symptoms, such as tremor, slow body movement and postural instability. It has been widely demonstrated that estrogens can exert protective effects on the dopaminergic nigrostriatal neurons against different toxins (Baraka et al., 2011; Campos et al., 2012; D'Astous et al., 2003; Jourdain et al., 2005; Sawada et al., 2002). Increasing evidence implicated the activation of the GPER in these protective estrogenic effects. Results from our group demonstrated that selective activation of the GPER using G1 protects rat midbrain dopaminergic neurons against MPP^+, a protection similar to that exerted by E_2. In addition, we observed that when E_2 was used in combination with G15 its protective effect was no longer observed (Bessa et al., 2015). Similar to E_2, treatment with G1 increases the concentration of dopamine, its metabolites, and the specific binding to the membrane (DAT) and vesicular (VMAT) dopamine transporters in the striatum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice. These dopaminergic protective effects of E_2 and G1 were lost in the presence of G15 (Bourque et al., 2013). Comparable protective effects in the striatum of MPTP-exposed mice mediated by GPER activation were also observed in other studies using treatment with either G1 (Bourque et al., 2015) or raloxifene (Bourque et al., 2014).

The dopaminergic protective actions promoted by GPER activation observed in the above-mentioned studies appear related to the ability of G1 to increase the expression of neurotrophic factors. We found that G1 is capable of inducing an increase in GDNF protein in midbrain neuron-glia cultures, and that GDNF neutralization or silencing in these cultures impedes the dopaminergic protective effect of GPER selective activation (Bessa et al., 2015). This was also observed by Cheng et al. (2017) on neuroblastoma cell line SH-SY5Y. G1 reduced the MPP^+-induced cell death through the increase of GDNF, effects that were abrogated by G15 (Cheng et al., 2017). In addition, it was observed by others that the protective effects promoted by GPER activation in the striatum of MPTP mice occurred in parallel with an up-regulation of BDNF and GDNF protein levels, increase in the anti-apoptotic Bcl-2 protein and activation of the pro-survival kinases Akt and ERK (Bourque et al., 2014, 2015). This suggests that protection mediated by GPER activation involves both inhibition of apoptosis and promotion of dopaminergic survival. Guan et al. (2017) showed that protection mediated by G1 in the MPTP mouse model involves also an anti-

inflammatory effect. G1 treated mice present a reduction in the number of microglial cells and IL-1β, TNFα and IL-6 protein and mRNA levels in the midbrain (Guan et al., 2017). In fact, although PD is essentially an idiopathic disease, it is accepted that inflammation promoted by microglial cells plays a critical role to the progressive dopaminergic neuronal death. GPER selective activation is associated with the modulation of inflammatory responses, with G1 inhibiting Lipopolysaccharide (LPS)-induced IL-6 expression in murine macrophage cells (Okamoto et al., 2017). A study from our group, demonstrated that G1 treatment protects dopaminergic neurons in the *substantia nigra*, an effect accompanied by decreased IL-1β, CD68 and Inducible nitric oxide synthase (iNOS) mRNA levels in this region. Moreover, we also demonstrated that G1 treatment prevents LPS-induced impairment of motor function (Mendes-Oliveira et al., 2017).

The above-mentioned effects were described on males. Data regarding the effects induced by GPER on females are scarce and contradictory. To our knowledge, the few studies that exist in PD models using female models were carried out with the administration of tamoxifen or raloxifene (Baraka et al., 2011; Dluzen and Mickley, 2005), two selective estrogen receptor modulators (SERMs) with antagonistic actions towards ERα and ERβ and acting as GPER agonists (Filardo et al., 2000; Meyer et al., 2011). Dluzen and Mickley (2005) demonstrate a protective role of tamoxifen from dopaminergic toxins, inducing an increase of striatal dopamine and 3,4-dihydroxyphenylacetic acid concentrations on females (Dluzen and Mickley, 2005). On the other hand Baraka et al. (2011) using a rat model of PD demonstrated that tamoxifen does not induce any protection in OVX females, whereas raloxifene protected striatal dopaminergic neurons against 6-OHDA-induced neurotoxicity (Baraka et al., 2011).

In conclusion, GPER is a promising therapeutic target for the treatment of PD. In males, the activation of GPER protects the dopaminergic neurons in the substantia nigra and the striatal nerve terminals, increases the concentration of dopamine and its metabolites, as well as DAT and VMAT-2 specific binding. GPER activation is also able to protect motor functions. (Table 3). These protective actions induced by the GPER activation involve an increase in the production of neurotrophic factors, the inhibition of apoptosis, promotion of survival, and reduction in inflammation. Besides the protective effects, it would be important to evaluate whether GPER activation has the ability to promote recovery or stop the progressive loss of dopaminergic neurons. There is no information on the selective activation of GPER in females, and the scarce information on the modulation of GPER refers to the use of non-selective agonists such as raloxifene and tamoxifen. In addition, the existing data is contradictory, making difficult to draw conclusions about the potential effects of GPER in female models of PD.

4.2.3. Multiple sclerosis

Multiple sclerosis (MS) is characterized by multiple focal areas of myelin loss within the CNS called plaques or lesions (Thompson et al., 2018). The hallmarks of MS pathology are axonal or neuronal loss, demyelination, and astrocytic gliosis (Thompson et al., 2018). Among these neuropathological characteristics, axonal loss is particularly relevant because it is the main underlying mechanism of permanent disability (Thompson et al., 2018). This axonal loss was associated with different mechanisms such as the energy deficit linked to mitochondrial dysfunction and the loss of trophic support (Thompson et al., 2018).

Wang et al. (2009) reported the ability of GPER activation to promote protection in MS using the rodent experimental autoimmune encephalomyelitis (EAE) model (Table 3). Selective activation of GPER with G1 reduced clinical and histological EAE signs, whereas E_2 mediated protection was significantly impaired in GPER gene-deficient female mice (Wang et al., 2009). The role of GPER in the EAE model is also supported by the finding that selective activation of GPER with G1 reduced the severity of disease in EAE models of MS and that this effect is concomitant with a G1-mediated decrease in pro-inflammatory cytokines, including Interferon γ (IFNγ) and IL-17 (Blasko et al., 2009). Furthermore, the results also showed the ability of G1 to inhibit the production of cytokines such as TNFα and IL-6 in a dose-dependent manner in human primary macrophages and in a murine macrophage cell line (Blasko et al., 2009).

Studies about the influence of ERα and GPER on E_2 ability to treat EAE showed that E_2 reduced disease severity in wild-type and ERα knockout female mice, but did not alter the disease in the GPER knockout group (Yates et al., 2010), suggesting that GPER is necessary for the protective effect mediated by E_2. Moreover, the effects on disease severity of both receptors were associated with the production of anti-inflammatory IL-10 following E_2 treatment (Yates et al., 2010).

GPER is expressed throughout the oligodendrocyte differentiation and promyelinating stages in primary oligodendrocyte cultures derived from rat spinal cords and brains (Hirahara et al., 2013). Additionally, it was also shown that selective activation of GPER with G1 enhanced oligodendrocyte maturation and remyelination after demyelination, suggesting an additional mechanism of protection triggered by GPER selective activation and enhancing the potential of GPER selective agonists as therapies for the treatment of MS (Hirahara et al., 2013).

It is also important to note that that results regarding the effects induced by the selective activation of GPER on *in vivo* MS models were carried out only in female models, therefore, it would be important to clarify if these effects also occur in males.

4.3. GPER in mood disorders

Mood disorders are common psychiatric illnesses characterized by conspicuous disturbances in emotional disposition, and include diseases such as depression or bipolar disorders (Marvel and Paradiso, 2004). In 2009, Xu et al. demonstrated that G1 attenuates serotonin receptor signaling in the paraventricular nucleus of the hypothalamus and reduces responses to oxytocin and adrenocorticotropic hormone, rising the hypothesis that GPER could play a role in mood disorders (Xu et al., 2009). On the other hand, GPER is necessary for E_2-induced changes in serotonin 1A receptor signaling (McAllister et al., 2012). Desensitization of serotonin 1A receptor is a key element for selective serotonin reuptake inhibitors (SSRI) efficacy in the treatment of mood disorders, and the expression of GPER shortens the onset of SSRI therapeutic effects in a GPER-dependent manner, thus providing evidences that GPER may accelerate the therapeutic effect of SSRI treatment in mood disorders (Table 4) (McAllister et al., 2012).

In a mouse model of depression, G15 inhibited the anti-depressant effects of G1 (Dennis et al., 2009). Studies on the impact of classical ER and GPER on SSRI treatment of depression in OVX female rats showed that long-term treatment with G1 induced anti-depressant-like effects associated with an increase in the phosphorylation levels of Akt, ERK and TrkB receptor in the hippocampus (Table 4) (Benmansour et al., 2016).

Evaluation of serum GPER levels in 38 euthymic bipolar disorder patients showed that both male and female patients had higher GPER levels than the respective control groups, while there were no differences in serum E_2 levels, suggesting that GPER may play a role in the pathophysiology of bipolar disorder (Orhan et al., 2018).

Anxiety disorders comprehend a wide range of disturbances that include panic disorders, obsessive-compulsive disorders, post-traumatic stress and generalized anxiety disorders (Somers et al., 2006). Kastenberger et al. (2012) demonstrated that short-term application of specific agonists of classical ER did not induce any behavioral changes, whereas specific stimulation with G1 in male and OVX female mice induced anxiogenic effects, suggesting that estrogen-induced anxiogenic-like effects were mediated mostly by GPER (Table 4) (Kastenberger et al., 2012). Studies using wild-type female and male mice and GPER knockout mice demonstrated that alterations in anxiety-like behavior were observed predominantly in male mice (Kastenberger and Schwarzer, 2014). In contrast, others reported data supporting

Table 3
Effects induced by GPER selective activation in neurodegenerative disorders.

	Major conclusions	Models	Reference
AD	Selective GPER activation ameliorated object recognition memory in female but not male mice;	5XFAD mice (intact female and male); Exposure to G1 and G15;	Kubota et al. (2016)
PD	Increased concentration of dopamine and its metabolites, and DAT and VMAT2 specific binding in the striatum; Increased DAT specific binding in the substantia nigra;	C57BL/6 mice (male); MPTP model; Subcutaneous injection of G1 twice daily for 10 days - before and after dopaminergic lesion;	Bourque et al. (2013)
	Increased dopamine and DOPAC concentration and specific binding of DAT and VMAT in the striatum; Increased anti-apoptotic Bcl-2 protein and activation of the pro-survival kinase Akt in the striatum;	C57BL/6 mice (male); MPTP model; Subcutaneous injection of raloxifene twice daily for 10 days - before and after dopaminergic lesion;	Bourque et al. (2014)
	Increased dopamine concentration and DAT and VMAT-2 specific binding in the striatum; Increased DAT specific binding in the substantia nigra; Increased GDNF, BDNF and Bcl-2 protein levels in the striatum;	C57BL/6 mice (male); MPTP model; Subcutaneous injection of G1 twice daily for 10 days - before and after dopaminergic lesion;	Bourque et al. (2015)
	Prevention of the dopaminergic neuron loss in a GDNF-dependent process;	Wistar rat midbrain neuron-glia cultures; MPP^+ model; Exposure to G1;	Bessa et al. (2015)
	Increased dopaminergic fibers density in the striatum; Prevention of the dopaminergic neurons loss in the substantia nigra; Decreased microglial cells number and IL-1β, TNF-α and IL-6 protein and mRNA levels in the midbrain;	C57BL/6 mice (male); MPTP model; Subcutaneous injection of G1 twice daily for 12 days - before and after dopaminergic lesion;	Guan et al. (2017)
	Prevention of the dopaminergic neurons loss in the substantia nigra; Protection of the motor functions; Decreased IL-1β, CD68 and iNOS mRNA levels in the substantia nigra;	C57BL/6 mice (male); Unilateral injections in the substantia nigra with LPS on 5th day of G1 treatment; Subcutaneous injection of G1 twice daily for 12 days - before and after dopaminergic lesion;	Mendes-Oliveira et al. (2017)
	G1 reduced the MPP^+-induced cell death through the increase of GDNF, effects that were abrogated by G15;	Neuroblastoma cell line SH-SY5Y; MPP^+ model; Exposure to G1;	Cheng et al. (2017)
MS	Selective GPER activation mediates protection against MS, which is significantly impaired in GPER gene-deficient mice;	C57Bl/6J mice (female); GPER KO mice; EAE; Exposure to G1;	Wang et al. (2009)
	Selective GPER activation reduces the severity of MS through the decrease of pro-inflammatory cytokines, including IFNγ and IL-17; G1 inhibits the production of cytokines such as TNFα and IL-6 in a dose-dependent manner;	Primary culture of macrophages, microglia and a murine macrophage cell line (RAW264.7); EAE; Exposure to G1;	Blasko et al. (2009)
	E_2 reduced disease severity in wild-type and ERα KO mice, but had no impact on GPER KO group; These different effects were associated to the production of anti-inflammatory IL-10; GPER have an important but still undefined role in regulating immune reactivity in MS severity;	C57Bl/6J mice (intact female); Ethinylestradiol treatment; WT, ERαKO and GPERKO mice;	Yates et al. (2010)
	GPER is expressed throughout oligodendrocyte differentiation and promyelinating stages; Selective GPER activation enhanced oligodendrocyte maturation and remyelination after demyelination;	Primary oligodendrocyte cultures from Wistar rat spinal cord; Demyelination model; Exposure to G1 and G15;	Hirahara et al. (2013)

anxiolytic effects of GPER in OVX female mice being this associated to the regulation of synaptic transmission in the basolateral amygdala (BLA) (Tian et al., 2013) and independent of ERK signaling (Anchan et al., 2014). A differential contribution of GPER in the control of anxiety in male and female mice is also supported by data from the elevated plus maze task showing that acute administration of G1 leads to anxiolytic effects in gonadectomized male mice, but not in female mice (Table 4) (Hart et al., 2014). Somehow, these results establish a parallelism with what has already been described for E_2 and ERα/ERβ (Hart et al., 2014). Being the nature of E_2 effects on anxiety attributable to the differential effects of specific estrogen receptor subtypes. ERβ activation induces anxiolytic-like effects whereas ERα activation appears to have mainly anxiogenic-like properties (Hart et al., 2014).

Chronic pain-related anxiety is attenuated by subcutaneous injection or local infusion of G1 in the basolateral amygdala in OVX female mice, being these effects associated with the prevention of imbalance between excitatory and inhibitory transmissions in the basolateral amygdala synapses (Liu et al., 2015).

Increased serum GPER levels might play a role in the etiology of generalized anxiety disorder. In a study involving 40 drug-naïve patients newly diagnosed with anxiety disorder there were significantly higher levels of GPER in the serum of patients with generalized anxiety disorder and a positive correlation between GPER serum levels and severity (Findikli et al., 2016).

The existing data indicates that for several disorders the effects triggered by GPER selective activation are dependent on the sex of animals, or with the amount of circulating E_2 levels. Due to the scarcity of studies regarding the selective activation of GPER in both males and females, it is not possible to establish a clear hypothesis to explain these differences. However, the differential effects can relate with the complex signaling pathways activated by GPER and to the crosstalk between estrogen receptors on males and females (Hart et al., 2014). Hart et al. (2014) showed that G1 increased protein expression of hippocampal phosphorylated ERα in male mice, but not in females (Hart et al., 2014). These modifications were associated with different anxiolytic effects in males and females (Hart et al., 2014). Although the differential effects observed upon GPER activation in males and females may involve similar effects the data currently available are insufficient to draw any conclusions.

Table 4
Effects induced by GPER selective activation in mood disorders.

	Major conclusions	Models	Reference
Mood disorder	Selective GPER activation attenuates 5-HT1A receptor signaling and accelerates the effects of SSRIs treatment of mood disorders;	Sprague-Dawley rats (intact female); Exposure to G1; GPER distribution:	Xu et al. (2009)
	GPER is necessary for estradiol-induced changes in the serotonin 1A receptor signaling pathway and desensitization;	Sprague-Dawley rats (intact female): GPR30 siRNAs to decrease GPR30 Expression;	McAllister et al. (2012)
Depression	Selective GPER activation has antidepressant properties, which were inhibited by G15;	C57Bl6 mice (OVX female); Exposure to G1 and G15;	Dennis et al. (2009)
	Long-term treatment with G1 induces anti-depressant-like effect;	Sprague Dawley rats (OVX female); Exposure to G1;	Benmansour et al. (2016)
Bipolar	Serum GPER levels in euthymic bipolar patients are higher than in controls;	38 patients diagnosed with Bipolar disorder (males and females); Quantification of GPER in serum	Orhan et al. (2018)
Anxiety	Estrogen-induced anxiogenic-like effects are mediated mostly by GPER;	C57Bl6 mice (intact and OVX females); Exposure to G1;	Kastenberger et al. (2012)
	GPER has a direct involvement in anxiety and stress control, being this impact stronger in male than in female mice;	C57BL/6J mice (male and intact female); GPER KO mice;	Kastenberger and Schwarzer (2014)
	The selective activation of GPER had an anxiolytic effect in the open field test;	C57BL/6J mice (OVX female); Exposure to G1;	Anchan et al. (2014)
	GPER selective activation has anxiolytic properties in gonadectomised male, but not in female mice;	C57BL/6J mice (gonadectomized males and intact females); Exposure to G1;	Hart et al. (2014)
	GPER selective activation induced anxiolytic effects in OVX female mice attributed to the maintenance of the balance between excitatory and inhibitory transmissions in the basolateral amygdala;	C57BL/6J mice (OVX female); Exposure to G1 and G15;	Liu et al. (2015)
	Serum GPER levels were significantly increased in patients diagnosed with generalized anxiety disorder, with a positive correlation between GPER levels and severity of the disease;	40 patients diagnosed with generalized anxiety disorder; Serum GPER quantification;	Findikli et al. (2016)

4.4. Autism spectrum disorder (ASD)

To the best of our knowledge, only one study investigated the impact of GPER in ASD. Data from the analysis of GPER serum levels in patients diagnosed with ASD indicate that ASD patients have significantly lower levels of GPER when compared to the control group (Altun et al., 2017). The results showed also a negative correlation between GPER levels and the Childhood Autism Rating Scale total score rising the hypothesis of a role of GPER in the etiology of ASD (Altun et al., 2017).

4.5. Spinal cord injury

SCI may result in severe dysfunction of motor neurons and consequently the protection and improvement of spinal motor neurons following SCI represents a priority (Thuret et al., 2006). GPER selective activation with G1 dose-dependently reduced neuron apoptosis and improved functional recovery following SCI in the weight-drop spinal cord contusion model in male rats, whereas GPER knockdown inhibited the beneficial actions of E_2, suggesting that GPER might be the main ER responsible for the neuroprotective effects induced by E_2 (Hu et al., 2012). Similar results were obtained in mice. GPER selective activation with G1 mimicked the effects of E_2 treatment and prevented SCI-induced apoptotic cell death and enhanced motor functional recovery after injury, whereas the neuroprotective effects of G1 and E_2 were blocked by G15 in adult female C57BL/6J mice (Cheng et al., 2016).

5. Conclusions

Here we reviewed the body of work that has been conducted over the latest years in an attempt to elucidate the role of GPER selective activation in brain physiology and physiopathology, particularly in neurological disorders. The data demonstrates that for several pathologies, like mood disorders, AD or PD, GPER selective activation could be an interesting therapeutic target to induce neuroprotection. Nevertheless, for others, as is the case of IS, the existing information is not consensual. Despite the promising beneficial effects observed in neurodegenerative disorders, the information that exists is still not enough. It is essential to further explore, clarify and characterize the molecular mechanisms that underlie those effects. In addition, it is crucial to highlight the effect of selective GPER not only on neurons, but also on other cellular populations that are present in the brain like glial and vascular cells.

Further studies are also necessary to elucidate the effects induced by GPER at the tissue level to clarify the impact that its activation has on different types of tissues, also exploring possible cell-type specific interactions within each tissue. On the other hand, it is also evident the need of studies regarding the role of GPER in the human CNS, as well as its modulation with selective or non-selective ligands. It is also important to understand the effects of GPER activation on other organs and to develop studies focusing on the pharmacokinetics and pharmacodynamics of GPER agonists and antagonists.

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