Functional role of translocator protein and its ligands in ocular diseases (Review)

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Abstract. The 18 kDa translocator protein (TSPO) is an essential outer mitochondrial membrane protein that is responsible for mitochondrial transport, maintenance of mitochondrial homeostasis and normal physiological cell function. The role of TSPO in the pathogenesis of ocular diseases is a growing area of interest. More notably, TSPO exerts positive effects in regulating various pathophysiological processes, such as the inflammatory response, oxidative stress, steroid synthesis and modulation of microglial function, in combination with a variety of specific ligands such as 1-(2-chlorophenyl-N-methylpropyl)-3-isoquinolinecarboxamide, 4'-chlorodiazepam and XBD173. In the present review, the expression of TSPO in ocular tissues and the functional role of TSPO and its ligands in diverse ocular diseases was discussed.

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Abbreviations: TSPO, translocator protein; OMM, outer mitochondrial membrane; VDAC, voltage-dependent anion channel; ANT, adenine nucleotide translocase; mPTPs, mitochondrial permeability transition pores; ROS, reactive oxygen species; NOX, NADPH oxidase; AD, Alzheimer's disease; PPIX, protoporphyrin IX; PK11195, 1-(2-chlorophenyl-N-methylpropyl)-3-isoquinolinecarboxamide; Ro5-4864, 4'-chlorodiazepam; DBI, diazepam-binding inhibitor; PIGAS, phenylindolyilglyoxylamydes; FGIN-1-27, N,N-di-n-hexyl 2-(4-fluorophenyl) indole-3-acetamide; PET, positron emission tomography; TNF-α, tumor necrosis factor-α; COX-2, cyclooxygenase-2; LPS, lipopolysaccharide; RGC, retinal ganglion cell; RPE, retinal pigment epithelium; AMD, age-related macular degeneration; CNV, choroidal neovascularization; DR, diabetic retinopathy; DM, diabetes mellitus

Key words: TSPO, ligand, ocular diseases

Contents

1. Introduction

Translocator protein (TSPO; 18 kDa) is a highly structurally conserved hydrophobic protein located on the outer mitochondrial membrane (OMM) (1). Discovered in the 1970s, TSPO was originally termed the 'peripheral benzodiazepine receptor' due to its specific binding site for certain benzodiazepines in peripheral tissues (2). In 2006, the name was changed to TSPO to reflect the cholesterol binding and transportation functions of the protein (3). TSPO is also involved in a variety of cellular physiological activities such as mitochondrial quality control, mitochondrial permeability transition pore opening, voltage-dependent anion channel (VDAC) opening, calcium transport, cellular proliferation, programmed apoptosis and reactive oxygen species (ROS) production (4-8). This extensive range of molecular functions has led to the association of TSPO with the pathogenesis of multiple diseases, including central nervous system diseases and cardiovascular anomalies (9-12). Increasing research interest in TSPO as a crucial pathogenic factor and therapeutic target has driven the study of TSPO-specific, high-affinity binding molecules, known as TSPO ligands. TSPO ligands have been shown to have a beneficial effect by agonizing or inhibiting TSPO activity in diseases such as Alzheimer's disease (AD), multiple sclerosis and cardiac arrhythmias (13-15). It was not until the previous decade, however, that the role of TSPO and its ligands in ocular diseases became an area of active research, and a number of promising developments have been identified (16-20). The present article provided a review of the advances in the study of TSPO and its ligands in ocular diseases. First, an overview of TSPO function was presented, and a variety of classical and novel TSPO ligands were described. Next, the expression of TSPO in ocular tissues based on existing studies

was summarized. Finally, the role of TSPO and its ligands in different ocular conditions was discussed, including ocular development and aging, age-related macular degeneration (AMD), retinal ischemia, diabetic retinopathy (DR) and glaucoma. The aim of the present review was to highlight the research value of TSPO in ophthalmology and to suggest perspectives on potential therapeutic targets.

2. Structure and distribution of TSPO

TSPO is a highly hydrophobic protein that is expressed in both prokaryotic and eukaryotic cells, from bacteria to humans (21). TSPO is primarily localized to the OMM, adjacent to the VDAC and adenine nucleotide translocase (ANT) (1,22,23). This 169-amino acid protein in humans is encoded by a nuclear gene containing four exons (24) and the mature protein contains five α-helical transmembrane domains (TMs). A cholesterol-recognition amino acid consensus sequence is located in the C-terminus of the TM structure, through which TSPO binds to the lipid membrane (25,26). The 3D structure of TSPO in complex with the TSPO-targeting ligand, (R)-1-(2-chlorophenyl-N-methylpropyl)-3-isoquinolinecarboxamide (PK11195), comprising five transmembrane helices (TM1-TM5) that tightly pack together in the clockwise order TM1-TM2-TM5-TM4-TM3 viewed from the cytosol, has also been revealed (26). TSPO is highly expressed in a variety of tissues, particularly in the gonads, adrenal glands, placenta and brain, due to its high abundance in steroidogenic cells (27). Therefore, the pathogenic effects of TSPO and the potential therapeutic value of TSPO ligands for anxiety disorders, AD and hypogonadism have been thoroughly investigated *in vitro* and *in vivo* (28-30).

3. TSPO is involved in multiple cellular functions

TSPO is involved in a large variety of physiological cellular processes (Fig. 1). First, the subcellular localization of TSPO dictates its critical role in mitochondrial function; it is a regulator of mitochondrial respiration, membrane potential, energy homeostasis and quality control (4,31-33). TSPO also reduces mitophagy, which inhibits essential ubiquitination of proteins, leading to a low efficiency of ubiquitin-dependent mitochondrial protein degradation, and thus, an accumulation of dysfunctional mitochondria (33). Previous studies have reported that TSPO modulates mitochondrial permeability transition pores (mPTPs), such as VDAC and ANT (1,5,9). However, there is conflicting evidence regarding these interactions, which suggests that TSPO is not a key mPTP regulator (8). Accordingly, these interactions remain ambiguous, and we hypothesized that these are possibly indirect or cell type-dependent. Another function of TSPO is to control intracellular signaling pathways between mitochondria and the nucleus, thereby affecting nuclear gene expression (6). Finally, TSPO is associated with multiple general cellular activities, such as cell proliferation, cell differentiation (34) and programmed cell death (35), and also acts as a gatekeeper for the biosynthesis of steroid hormones (8). TSPO is involved in the translocation of cholesterol and porphyrins from the outer to the inner mitochondrial membrane (22), which is a rate-limiting step in steroid and neurosteroid synthesis (36). TSPO also regulates calcium ion homeostasis in cells and activates calcium-dependent NADPH oxidase (NOX) (37), thereby increasing ROS levels (38,39). An additional study has demonstrated that TSPO is a key regulator of NOX1-dependent neurotoxic ROS production (40). In fact, the function of TSPO is still regarded as debatable, and thus, more future studies are required to elucidate this. For example, one of the most highly researched areas of TSPO is its key role in steroidogenesis. However, Tu *et al* (28,29) successfully established a TSPO systemic knockout mouse model and demonstrated that TSPO is not essential for steroidogenesis. In addition, some studies solely focused on TSPO ligand functions without measuring TSPO levels, thus it remains unclear whether TSPO had a direct impact on the biological events (14,25). Therefore, further experiments are required to explain the aforementioned unclear mechanisms in order to ascertain the role of TSPO.

4. TSPO ligands

TSPO ligands. TSPO ligands are classified as endogenous or synthetic ligands. In previous years, TSPO-ligand interactions have received increasing attention, with multiple studies reporting its positive effects on diseases such as AD, multiple sclerosis, anxiety and vasculopathy (13-15,41). Steroidogenesis and anti-inflammation are the main pathways by which TSPO ligands function (42). However, the independent mechanism, 'mitohormesis', defined as subtoxic stress on mitochondria, may be responsible for the protective effects of TSPO ligands. It is proposed that the ligands suppress ATP synthesis through mitohormesis, leading to activation of the cellular damage-response network. This, in turn, enhances the tolerance of cells to the degeneration processes, including oxidative damage, phototoxicity or DNA damage (43). A summary of classical and novel ligands and their features and effects based on existing studies is described below and in Table I.

Porphyrins. Porphyrins are high-affinity endogenous ligands for TSPO, in the micromolar to nanomolar range (35). Mitochondria are critically involved in porphyrin metabolism and TSPO is closely related to this process (26,44). Porphyrins are involved in heme synthesis, and protoporphyrin IX (PPIX), as a key intermediate in the heme biosynthesis pathway, has been one of the most extensively studied endogenous ligands since its discovery in 1987 (45,46). Previous studies have reported that TSPO-PPIX interactions regulate mitochondrial membrane permeability and thus exert cytoprotective effects (46,47). Porphyrin-induced oxidative stress is thought to be the major mechanism of porphyrin-mediated tissue damage (39,48). Furthermore, Yamamoto *et al* (49) demonstrated that TSPO knockdown leads to the accumulation of PPIX and ROS in glioblastoma cells. Specifically, TSPO possibly functions by binding or sequestering PPIX rather than via TSPO-mediated transmembrane transport (50). Unbound PPIX inhibits heme oxygenase and prevents free heme degradation, thereby maintaining the balance between free and bound heme and preventing cytotoxic effects (51).

PK11195. PK11195 was the first non-benzodiazepine TSPO synthetic ligand discovered that acts in the nanomolar

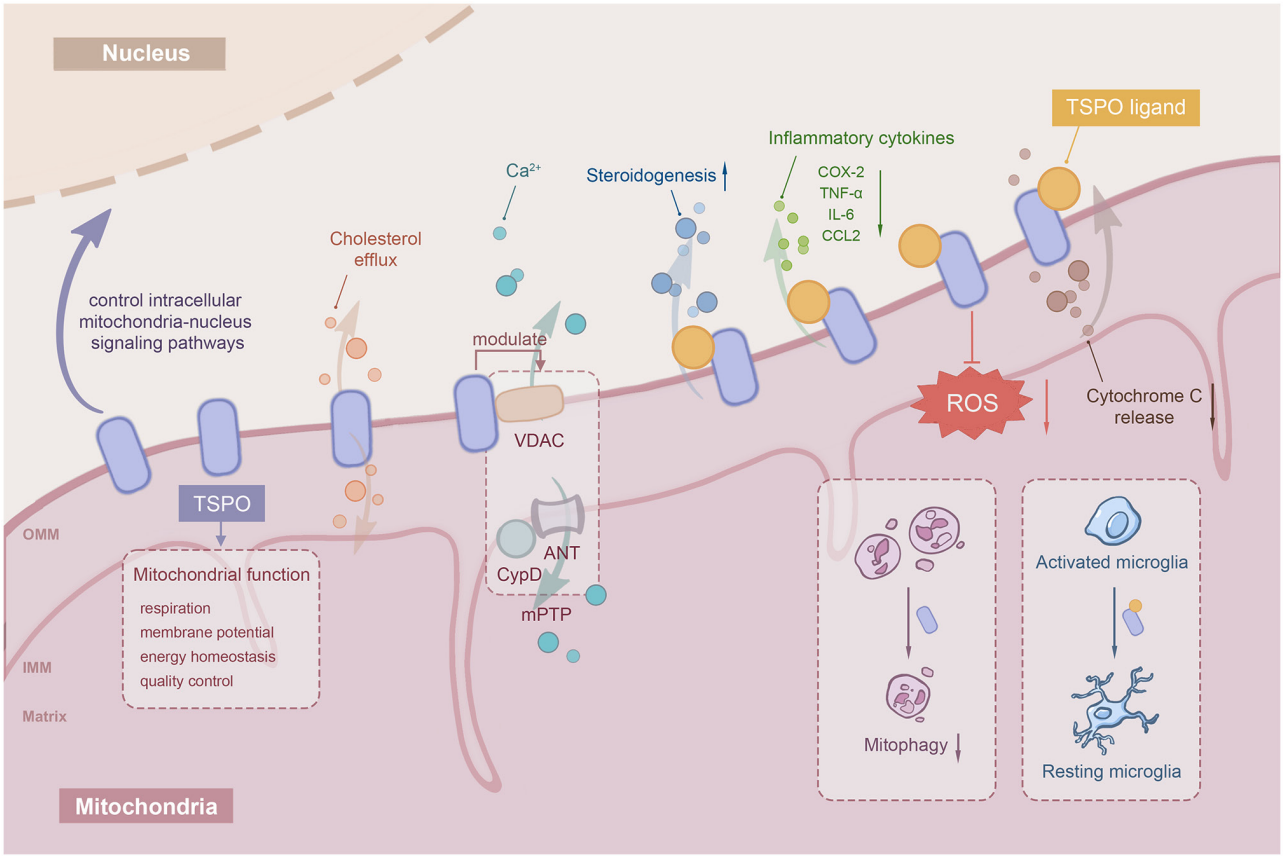

Figure 1. Diagram summarizing the key functions of TSPO and TSPO ligands. TSPO is located in the OMM. TSPO reduces mitophagy and is a regulator of multiple mitochondrial functions including mitochondrial respiration, membrane potential, energy homeostasis and quality control. TSPO controls signaling pathways between mitochondria and the nucleus and thereby affects nuclear gene expression. TSPO is involved in the cholesterol transport from the OMM to the IMM. The close apposition of TSPO and mPTP complexes enables TSPO to regulate the function of mPTP, thereby affecting Ca^{2+} transport across the OMM and maintaining Ca^{2+} homeostasis. TSPO ligands modulate TSPO and promote cell steroidogenesis, downregulate cell inflammatory cytokine expression, decrease ROS production as well as induce the switching of microglia from the active state to favor the resting state. TSPO ligands reduce cytochrome c release from mitochondria to the cytoplasm, thereby inhibiting the mitochondrial apoptosis pathway. OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; VDAC, voltage-dependent anion channel; ANT, adenine nucleotide translocase; CypD, cyclophilin D; mPTPs, mitochondrial permeability transition pores; ROS, reactive oxygen species; TSPO, translocator protein; COX-2, cyclooxygenase-2; TNF-α, tumor necrosis factor-α; IL, interleukin; CCL2, C-C motif chemokine receptor-2.

range (42). PK11195 is considered one of the best-characterized and prototypic ligands of TSPO (50), and is widely used to study the roles and functions of TSPO in various diseases, particularly in *in vivo* studies. [^{11}C]PK11195 has been additionally applied as a radioligand for positron emission tomography (PET). Despite several limitations, such as poor brain permeability, kinetic instability and signal-to-noise ratio issues due to non-specific binding (52-54), [^{11}C]PK11195 remains the standard TSPO-based PET radiotracer for assessing the activation of microglia or macrophages in central nervous system disorders (55,56). PK11195 has also been reported to have anti-neuroinflammation effects in experimental models of AD (10) and pressure-induced retinal ganglion cell (RGC) injury (57). However, further research is needed to elucidate the specific mechanisms underlying these protective effects, including whether they are related to the stimulation effect on steroidogenesis in peripheral tissues and the brain (10,58). PK11195 downregulates the expression of the inflammatory cytokines, tumor necrosis factor-α (TNF-α) and cyclooxygenase-2 (COX-2), in lipopolysaccharide (LPS)-induced human microglia (59,60), and modulation of Ca^{2+}-mediated signaling pathways may be involved in its anti-inflammatory actions (61). In prostate cancer cells, PK11195 can be used as a sensitizer to the chemotherapy agents mda-7/IL-24 (Ad.mda-7, a novel cytokine gene belonging to the IL-10 gene superfamily) (62), both *in vitro* and *in vivo*. PK11195 promotes cellular autophagy by inactivating the oncoprotein, B-cell lymphoma-2, and by targeting F_1F_0-ATP synthase (63), an essential component of mPTPs (64). Notably, Gonzalez-Polo *et al* (65) reported that PK11195 promotes starvation-induced cell death through an unexpected pathway independent of TSPO, which directly activates the mitochondrial apoptotic pathway, as demonstrated by cytochrome c release and caspase-3 activation. Although PK11195 is generally considered to be a TSPO antagonist, there is evidence that PK11195 displays a partial agonistic effect on TSPO (66), which is possibly dependent on the cell type and drug concentration.

4'-chlorodiazepam (Ro5-4864). Ro5-4864 is another classical synthetic TSPO ligand that has been used to investigate the characteristics of TSPO in health and disease due to its nanomolar selectivity (67,68). However, the application of Ro5-4864 as a pharmacological agent (67) is limited as its affinity varies with species, from rat (high affinity) to human

Table I. Involved pathways or biological effects of TSPO ligands in *in vitro* and *in vivo* experimental models.

First author/s, year	TSPO ligands	Cell line/animal model	Findings of involved pathways/biological effects	(Refs.)
Yamamoto *et al*, 2014	PPIX	TSPO-knockdown glioblastoma cells	TSPO deletion leads to the accumulation of PPIX and ROS	(49)
Girard *et al*, 2012; Ravikumar *et al*, 2016; Choi *et al*, 2002	PK11195	LPS-induced human microglia	Downregulates the expression of TNF-α and COX-2, probably relevant to Ca^{2+}-mediated signaling pathways	(59-61)
Seneviratne *et al*, 2012		HeLa cells	Regulates cellular autophagy by targeting F_1F_0-ATP synthase, which is a TSPO-independent pathway	(63)
Ishikawa *et al*, 2016		Rat *ex vivo* glaucoma model	Inhibits pressure-induced RGC apoptosis by promoting the TSPO-5αRD-mediated AlloP synthesis	(57)
Gut *et al*, 2013	Ro5-4864	Isoprenaline-induced zebrafish larvae	Reverses the glucose level fluctuations	(70)
Bernardi *et al*, 2022; Baez *et al*, 2017		Glucose deprivation treated T98G astrocyte cells	Maintains mitochondrial homeostasis by reducing the production of free radicals and inhibits the mitochondrial apoptosis pathway by reducing cytochrome c release and caspase-3 activation	(36,74)
Da Pozzo *et al*, 2015		AD mouse model	Modulates the production of steroids to exert neuroprotective effects	(71)
Musman *et al*, 2017		Type-2 diabetes mellitus rat models	Limits cholesterol transport into mitochondria, inhibits oxysterol accumulation and reduces oxidative stress	(139)
Nothdurfter *et al*, 2012	XBD173	Anxiety disorder population and mouse model	Exerts anxiolytic properties by enhancing neurosteroidogenesis, thereby potentiating GABA-mediated inhibitory postsynaptic currents	(75)
Scholz *et al*, 2015		Retinal degeneration mouse model	Alleviates neurodegeneration by targeting the microglia/macrophage marker, CD68, and reducing the levels of pro-inflammatory factors, CCL2 and IL-6	(78)
Mages *et al*, 2019		Retinal ischemia mouse model	Reduces microglia and promotes the transformation toward the anti-inflammatory M2 phenotype, thereby protecting inner retinal neurons	(18)
Lieth *et al*, 1998; Wagner *et al*, 2017; Delyfer *et al*, 2005		Retinal degeneration/ischemia mouse model	Maintains the metabolism of the 'neuron-supportive microenvironment' and protects against neurotoxic injury by regulating glutamine synthetase expression	(123,124,126)
Wolf *et al*, 2020; Nagineni *et al*, 2012		Laser-induced CNV mouse model	Inhibits the generation of CNV by inhibiting pro-angiogenic factor and autocrine, IL-1β, regulating phagocytosis and facilitating the transition of microglia to neuroprotective phenotypes	(40,116)
Biswas *et al*, 2021; Ibrahim *et al*, 2020	Etifoxine	High-fat diet/obesity mouse model	Enhances cholesterol metabolism by downregulating the total cholesterol, triglyceride and phospholipid mass both in RPE and in serum	(84,85)
Biswas *et al*, 2018; Biswas *et al*, 2017		Choroidal endothelial cells (RF/6A)	Inhibits apoptosis by reducing intracellular lipid accumulation, ox-LDL-induced ROS production and inflammatory cytokine secretion	(17,25)
Wang *et al*, 2014	DBI/TTN	Retinal inflammation mouse model	DBI-TSPO signaling limits the magnitude of microglial activation and promotes a return to baseline quiescence through macroglia-microglia interactions	(16)

Table I. Continued.

First author/s, year	TSPO ligands	Cell line/animal model	Findings of involved pathways/biological effects	(Refs.)
Santoro *et al*, 2016	PIGAS	INFγ/LPS-induced rat C6 glioma cells	Downregulates pro-inflammatory enzymes, iNOS and COX-2, expression by modulating neurosteroid synthesis	(91)

TSPO, translocator protein; PPIX, protoporphyrin IX; ROS, reactive oxygen species; PK11195, 1-(2-chlorophenyl-N-methylpropyl)-3-isoquinolinecarboxamide; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-α; COX-2, cyclooxygenase-2; RGC, retinal ganglion cell; 5αRD, 5α-reductase; AlloP, allopregnanolone; Ro5-4864, 4'-chlorodiazepam; AD, Alzheimer's disease; CCL2, C-C motif chemokine receptor-2; IL-6, interleukin 6; RPE, retinal pigment epithelium; ox-LDL, oxidized low-density lipoprotein; CNV, choroidal neovascularization; DBI, diazepam-binding inhibitor; TTN, triakontatetraneuropeptide; PIGAS, phenylindolyilglyoxylamydes; INFγ, interferon γ; iNOS, inducible nitric oxide synthase.

(low affinity) (21). Another limitation is that the affinity of [^{3}H] Ro5-4864 can be influenced by temperature, as found in brain membrane binding assays (69). Gut *et al* (70) reported that Ro5-4864 is sufficient to reverse the glucose level fluctuations induced by isoprenaline in zebrafish larvae, suggesting that Ro5-4864 may influence glucose homoeostasis in response to altered mitochondrial energy balance. Ro5-4864 also has certain features that are similar to that of PK11195. For example, Ro5-4864 stimulates steroid formation (10), contributes to the neuroprotective effect (but differentiates from PK11195 activity under different experimental conditions) (71) and inhibits pro-inflammatory factors and ROS production in human microglia incubated with LPS (16,59). Furthermore, Ro5-4864 antagonizes the anxiolytic and antidepressant-like effects of other TSPO ligands. For example, the antidepressant properties of PK11195 induced in mice subjected to the forced swimming test was blocked by Ro5-4864 administration (72,73). Ro5-4864 has also been shown to contribute to the maintenance of mitochondrial homeostasis, reducing cytochrome c release and caspase-3 activation, thereby inhibiting the mitochondrial apoptosis pathway (36). Furthermore, Baez *et al* (74) demonstrated that Ro5-4864 maintains mitochondrial function in the T89G astrocyte cell line in the presence of glucose deprivation damage by reducing the production of free radicals.

XBD173. XBD173 (AC-5216; Emapunil) is a novel high-affinity and selective phenylpurine ligand of TSPO, which has been well investigated and widely used in the research and therapy of anxiety disorders (41,75,76). GABA-mediated inhibitory postsynaptic currents were potentiated by XBD173 in both animal experiments and clinical studies (75), and this neurotransmission appeared to be mediated indirectly through the generation of neurosteroids and could be prevented by the 5α-reductase inhibitor, finasteride (76). According to previous studies, the role of XBD173 in microglia has been well defined and has been shown to alleviate the neurotoxic effect of microglia and inhibit cell proliferation and migration (16,77). The XBD173/TSPO axis appears to target the microglia/macrophage marker, CD68, and inhibit the pro-inflammatory genes, C-C motif chemokine receptor-2 and interleukin (IL-)6, to alleviate apoptosis, thereby alleviating neurodegenerative dysfunction (78). Mages *et al* (18) further investigated the exact response patterns of the major glial cell types of the retina in a retinal ischemia mouse model. In the study it was reported that XBD173 treatment resulted in lower microglia accumulation, and the microglial activation profile showed a transformation towards the anti-inflammatory M2 phenotype. However, the aforementioned effects of XBD173 on microglia could be reversed to some extent, since the reduced microglial cell number induced by XBD173 could transiently rise again (18). In addition, even with XBD173 intervention, cellular morphological changes (from ramified to amoeboid) representing microglial activation were observed, suggesting that XBD173 only partially inhibits microglial activation (18).

Etifoxine. To the best of our knowledge, Etifoxine (etafenoxine; Stresam®) is currently the only commercially available TSPO ligand (79). Etifoxine was developed in the 1960s for anxiety disorders and is administered for this purpose in >42 different countries (80). However previous studies have since reported its therapeutic potential in peripheral nerve injury and demyelination, and chemotherapy-induced pain (14,80,81). As a non-benzodiazepine anxiolytic, etifoxine appears to exercise its functions by binding to the β2 or β3 subunits of the $GABA_A$ receptor complex (82). Etifoxine also regulates $GABA_A$ receptors indirectly by stimulating neurosteroid production in both the central and peripheral nervous systems (24,83). Furthermore, Biswas *et al* (84) suggested that etifoxine modulates cholesterol homeostasis, promoting cholesterol efflux and transporting cholesterol to the liver, which is the most important function of this ligand. The authors also found that etifoxine enhanced the expression of cholesterol metabolism and transport enzymes in high-fat diet mice and significantly decreased the total cholesterol, triglycerides and phospholipid mass in the retinal pigment epithelium (RPE). This finding was consistent with that of a study by Ibrahim *et al* (85), which suggested that serum lipid levels were downregulated in etifoxine-treated mice. Furthermore, etifoxine leads to a higher conversion of cholesterol into high-density lipoprotein while preventing intracellular lipid accumulation, and therefore protecting cells against apoptosis by inhibiting oxidized low-density lipoprotein-induced ROS production and inflammatory cytokine secretion (17,25). In addition, etifoxine

stimulates neurosteroid synthesis; however, Costa *et al* (86) suggested that this effect depends more on residence time at the TSPO binding site rather than the binding affinities.

Other reported TSPO ligands. Diazepam-binding inhibitor (DBI) is an endogenous agonistic ligand of TSPO (3). DBI-TSPO interactions have been demonstrated to occur in the production of steroids such as pregnenolone, in both *in vivo* and *in vitro* experiments (87,88). DBI or its cleavage product, triakontatetraneuropeptide, binds to TSPO during a form of macroglia-microglia interaction, limiting the magnitude of microglial activation and promoting a return of microglia to the resting state, which is a hallmark of the down-regulation of inflammation (16). Novel TSPO synthetic ligands include N,N-di-n-hexyl 2-(4-fluorophenyl) indole-3-acetamide (FGIN-1-27), 7-chloro-N,N,5-trimethyl-4-oxo-3-phenyl-3,5-dihydro-4H-pyridazino(4,5-b)indole-1-acetamide (SSR180575) and phenylindolyilglyoxylamydes (PIGAS), all of which possess steroidogenic properties (12) and promote cholesterol metabolism and transporter gene expression (25). SSR180575 is anti-apoptotic and protects mitochondria against dysfunction in ischemia-reperfusion injury models (89,90). PIGAS displays anti-inflammatory capacity, as evidenced by decreased inducible nitric oxide synthase and COX-2 expression, possibly by modulating astrocyte function through neurosteroid synthesis (91).

5. Functional roles of TSPO and TSPO ligands in ocular diseases

Overview. Next, the expression of TSPO in ocular tissues, the mechanisms by which TSPO is involved in the progression of various ocular diseases (Fig. 2) and the role of TSPO ligands in therapeutic interventions are discussed, based on existing studies.

Current status of research on TSPO expression in ocular tissues. In recent years, the role of TSPO in ocular diseases has gained attention. However, it must be acknowledged that the number of studies on TSPO expression in ocular cells and tissues has been limited. Biswas *et al* (17,25) reported high TSPO expression in the RPE and choroidal endothelium of mice. This observation was consistent with that of a study by Mages *et al* (18), in which specific cell types were enriched via immunomagnetic separation and then protein expression levels were measured using mass spectrometry analysis. It was noted that TSPO was most highly expressed in RPE cells, vascular cells and Müller cells, while expression was lower in microglia and almost undetectable in retinal neurons (16,18,77). By contrast, Biswas *et al* (17) reported strong TSPO signals in the ganglial cell layer by immunofluorescence analysis in mouse eye sections. Differences in TSPO expression and localization may be due to differences in sample collection and immunoassay approaches. In addition, TSPO expression has been detected in human retina and RPE (77,92,93), with both containing high expression at the mRNA level. When the central and peripheral sections of the retina and RPE were isolated separately, the peripheral RPE exhibited higher TSPO expression than the central RPE (92). It remains unclear whether this infers any functional implications. To the best of our knowledge, there have been no further reports of TSPO expression in other ocular structures such as the cornea, conjunctiva, lens, meibomian gland and lacrimal gland.

TSPO in ocular development and aging. Wang *et al* (16) investigated whether the endogenous functions of TSPO expression are relevant to retinal developmental processes. TSPO is expressed in microglia with an amoeboid phenotype that invades the neural retina during early development. In adulthood, as microglia undergo a morphological transformation to a ramified cell shape, TSPO expression is barely detectable (94). There are several theories that might help explain this, including that TSPO is possibly involved in the physiological processes of microglial development (95,96), such as complement-mediated synapse elimination and phagocytosis of dead neurons (66). Temporary expression of TSPO may also be associated with the migration process of microglia during retina development (97), and the expression terminated when microglia reach the final site. On the other hand, certain researchers suggest that TSPO is unnecessary for healthy development and aging following the study of several generated systemic TSPO-knockout mouse lines (28,98,99). For example, Klee *et al* (92) considered that ocular development is not strongly associated with TSPO expression as no ocular phenotype was observed in TSPO-knockout mice aged 0-48 weeks old. Furthermore, TSPO mRNA expression did not show significant differences in human retina and RPE tissues among different age groups of donors (from 17-90 years old) (92), suggesting that TSPO expression may not be involved in the regulation of normal development and aging. These differential findings led us to consider whether there are compensatory mechanisms for TSPO deletion in the knockout models such that marked phenotypes are not evident during the development process. Furthermore, as a stress-related protein, the regulatory effects of TSPO in multiple pathways may be more critical in disease states but not play a major role in normal physiological development. At present, the potential mechanisms remain to be validated by additional studies.

AMD. AMD is a prevalent cause of severe visual impairment among elderly individuals (100). Clinically, AMD can be categorized into two subtypes: Dry AMD, which accounts for 80-85% of cases and manifests as geographic atrophy, and wet AMD, which accounts for 15-20% of cases and presents as neovascularization (101). The pathogenesis of AMD is multifaceted, with a combination of genetic and environmental factors, while the efficacy of existing therapies is extremely limited since there is no treatment available to prevent the irreversible degeneration of the photoreceptors that leads to loss of central vision (102,103). Dysfunctional cholesterol metabolism is one of the prominent mechanisms underlying the development of AMD (103). The pathological examination of patients with AMD has revealed subretinal deposits of apolipoproteins, cholesterol and cholesteryl ester, indicating a potential association of cholesterol transport disorders in AMD (17,104). Notably, the formation of drusen is associated with poor choroidal endothelial structural and functional integrity, resulting in inadequate nutrient and oxygen delivery to the RPE and photoreceptor cells and impairing their metabolite clearance (105). These processes are particularly associated with the

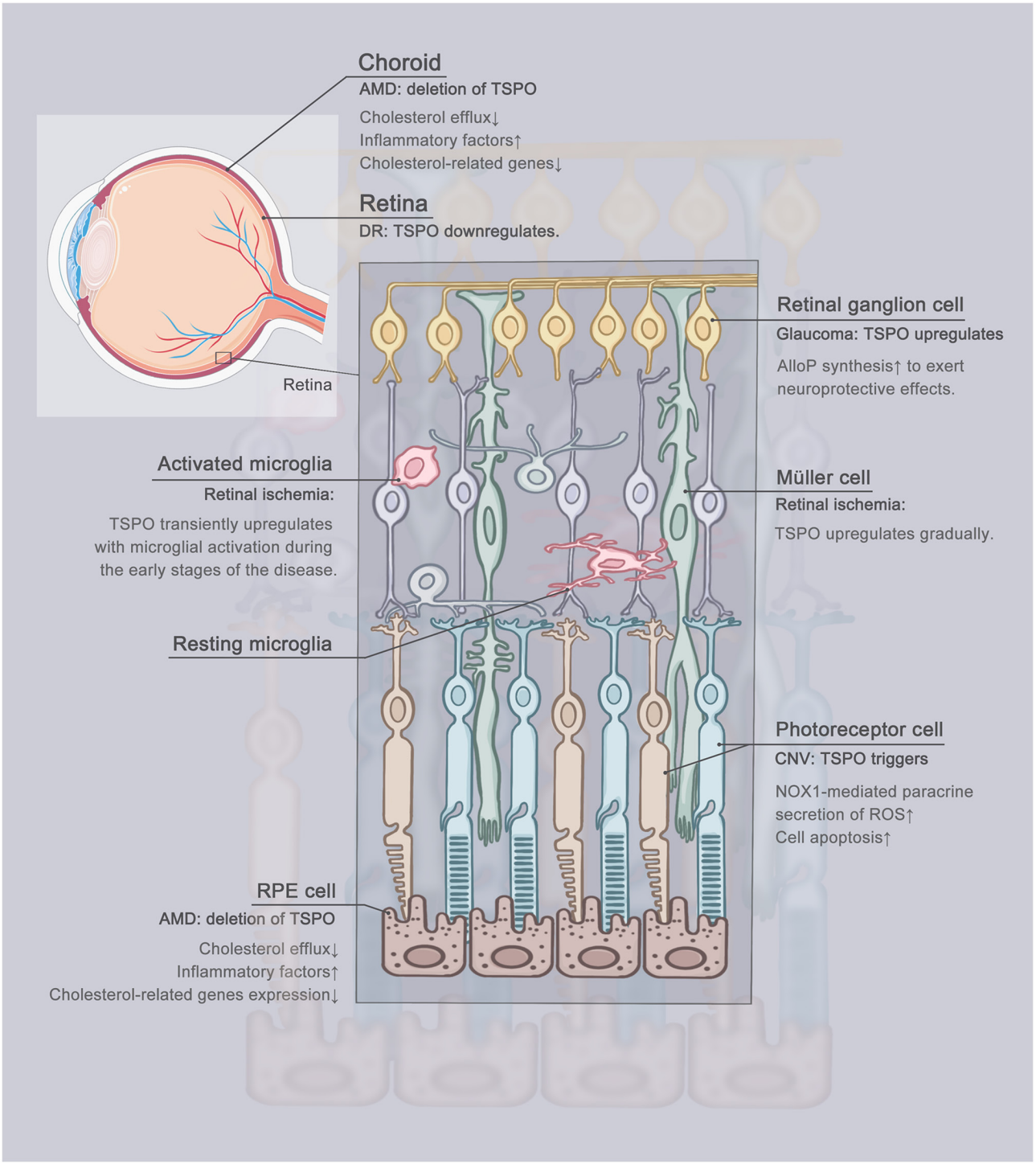

Figure 2. Affected areas or cell types associated with TSPO in various ocular diseases. TSPO, translocator protein; AMD, age-related macular degeneration; DR, diabetic retinopathy; AlloP, allopregnanolone; CNV, choroidal neovascularization; NOX1, NADPH oxidase 1; ROS, reactive oxygen species; RPE, retinal pigment epithelium.

pathogenesis of wet AMD (105,106). Aberrant expression of cholesterol homeostasis genes may lead to cholesterol and lipid dysregulation, thereby worsening AMD progression (107,108). This has been demonstrated in several experimental animal models showing AMD lesion progression (107,109,110). In addition, the release of inflammatory factors, the accumulation of ROS and the phagocytosis of neurons are involved in photoreceptor apoptosis in AMD (111-113). TSPO-knockout mice exhibit AMD-like features, including impaired cholesterol efflux, increased cholesterol, triglycerides and phospholipids in the RPE and choroid, increased levels of inflammatory factors (IL-1β and TNF-α) and downregulation of cholesterol-related genes (Nr1h3, Abca1, Abcg1, Cyp27a1 and Cyp46a1) (114). In a laser-induced choroidal neovascularization (CNV) model, TSPO regulated NOX1-mediated paracrine secretion of ROS, which is a crucial pathway for promoting pro-photoreceptor cell apoptosis (40). By contrast, angiogenic factors are generated via a non-NOX-dependent pathway, which can

be reversed by TSPO ligand treatment (115). These findings suggest that TSPO deficiency may contribute to the core pathogenesis of AMD. The TSPO ligand, etifoxine, upregulated cholesterol homeostasis gene expression in both RPE and choroidal vascular endothelial cells, promoting cholesterol efflux in a mouse AMD model (25,84). In addition, in human RPE cells (ARPE-19 cells), the FGIN-1-27, XBD173 and etifoxine ligands also significantly promote cholesterol efflux, whereas in TSPO knockdown RPE cells, this therapeutic effect is reversed (17). The aforementioned results imply that targeting the TSPO-mediated cholesterol efflux process may be effective in improving subretinal lipid accumulation in AMD. ROS production in RPE and choroid endothelial cells is also downregulated following etifoxine treatment (84). For neovascular AMD, XBD173 treatment inhibits the generation of CNV, which is thought to be associated with inhibiting pro-angiogenic factor (Vegf, Ang1 and Ang2) expression, regulating phagocytosis and facilitating the transition of microglia to neuroprotective phenotypes (40). In addition, inhibition of autocrine IL-1β levels in RPE, which has previously been shown to induce VEGF production, also provides a similar protective effect (116). In general, the mechanisms by which CNVs are formed are complex, and it is likely that TSPO ligands do not inhibit CNVs via a single pathway; thus, specific mechanisms warrant further exploration.

Retinal ischemia. Retinal ischemia is a major cause of visual impairment, often leading to irreversible morphological and functional injuries with depleted ATP stores (117). Extensive research has been devoted to clarifying the mechanisms of ischemia-induced neuronal damage, although debates persist. Retinal ischemic injury involves a cascade of self-reinforcing and destructive events, including neuronal depolarization, calcium imbalance and oxidative stress due to increased energy depletion and enhanced glutamate stimulation (118-121). TSPO was discovered to be upregulated in microglia during the early stages of retinal ischemia injury, which then decreased 4 days later (16). TSPO expression increases over time in Müller cells, which is the primary immune cell type in the retina, indicating an association between TSPO and the active retinal immune response during ischemic injury (16,18). A number of studies have shown that TSPO is closely associated with microglial activation and microglial energy metabolism (98,122). Thus, the transient increase in TSPO expression may be due to a microglia-mediated immune response or an acute response to an imbalanced energy supply in the postischemic phase. Furthermore, mice treated with the TSPO ligand, XBD173, have a significant reduction in neuron death in the postischemic retina. In addition, they have a decreased microglial number accompanied by phenotypic transformation from the M1 type to the M2 type, indicating anti-inflammatory activation (18). This finding concurred with those of Wang *et al* (16) and Karlstetter *et al* (77), who found that XBD173 inhibited microglial neurotoxicity and proliferation. The effect of XBD173 on Müller cells was also notable since it increased the level of DBI in postischemic Müller cells (18). As aforementioned, DBI an endogenous TSPO ligand, can alleviate neuroinflammation and induce microglia to favor the resting state (16). XBD173 regulates glutamine synthetase expression, thereby maintaining the metabolism of a 'neuron-supportive microenvironment' and protecting against glutamate-overload induced neurotoxic injury (123-126). It should be noted that the aforementioned effect of XBD173 was incomplete, as the transient upregulation of inflammatory markers as well as the downregulation of glutamine synthetase were still detected following XBD173 therapy. Given the high abundance of TSPO in the RPE, its role in retinal ischemia injury should not be overlooked. However, to the best of our knowledge, no relevant studies on the association between TSPO and RPE injury in retinal ischemia have been published to date. In summary, TSPO is involved in the pathogenic reactions of specific cell types to retinal ischemia and XBD173 treatment increased retinal neuron survival, to a certain extent.

DR. DR is the most prevalent complication of diabetes mellitus (DM) (127) and adversely affects the vision of working-aged individuals (128,129). The pathogenesis of DM and DR is complicated and unclear and treatment remains challenging due to recurrent vitreous hemorrhage and progressive loss of function (121). Hyperglycemia is considered to be a leading cause of metabolic disorders in the retinal vasculature via various pathways (130), including the protein kinase C, polyol and hexosamine pathways (131,132). Inflammation and dysfunction of glial cells are also involved in the onset and progression of DR (133,134). Other reported mechanisms of DR include mitochondrial dysfunction and oxidative stress damage, both of which accelerate retinal neuronal apoptosis (135-137). Correspondingly, TSPO has been suggested to play a role in the regulation of glucose metabolism, and the TSPO ligands, Ro5-4864 and PK11195, were both found to reduce the overall glucose levels in zebrafish larvae (70). Moreover, activation of TSPO regulates glucose homeostasis in adipocytes and it has been suggested that the TSPO ligands, PK11195 and FGIN-1-27, increase adipogenesis and glucose absorption by regulating mitochondrial activity and cholesterol transport (138). In addition, Ro5-4864 protects rat models of type-2 DM from metabolic disorders by limiting cholesterol transport into mitochondria, lowering oxysterol accumulation and reducing oxidative stress (139). Furthermore, TSPO relieves diabetic neuropathy by reportedly raising neuroactive steroid levels (11). Thus, TSPO has been identified as a potential target for diabetes management. Despite the increasing number of studies regarding the association between TSPO and DM complications, few investigations on the mechanism of TSPO in DR have been conducted. Zhou *et al* (20) found that TSPO was downregulated in rat models of type-2 DM 12 weeks after commencement of disease modeling. TSPO has previously been proposed to be an appropriate candidate marker of microglial activation (16); it was shown to be transiently upregulated in the early stages of retinal injury along with stress-induced microglial activation, while its expression was lower than that of controls or even absent after microglia returned to a resting state (140,141). Therefore, Zhou *et al* (20) hypothesized that the downregulation of TSPO in the retina indicated the activation of microglia in the retina during the early stages of diabetes. However, this hypothesis requires further study, as microglial activation was not consistently observed in the diabetic models, nor were changes in TSPO expression levels. Guo *et al* (19) reported significantly higher expression levels of TSPO in the peripheral blood of patients

with diabetes than in the controls, and a higher TSPO level in the active proliferative DR subgroup than in the inactive proliferative DR subgroup. Moreover, Guo *et al* (19) found that the TSPO/VDAC complex positively associates with several inflammatory cytokines, such as NOD-like receptor pyrin domain-containing 3, suggesting an important role in DR development and progression.

Glaucoma. Glaucoma is a leading cause of irreversible blindness worldwide and is characterized by progressive optic nerve injury and visual field loss (142,143). Glaucoma is a multifactorial disorder and elevated intraocular pressure is thought to be a major risk factor, leading to morphological deformation of the lamina cribrosa and disturbance of axoplasmic transport in RGC axons (144). Acute or chronic deficiency of these RGC neurotrophic signals ultimately leads to apoptosis (144). Other related pathogeneses of glaucoma include ocular hemodynamic abnormalities, low intracranial pressure, autoimmune dysfunction and mitochondrial dysfunction, while further studies are needed to investigate the detailed mechanisms of RGC injury (145). The neurosteroid, allopregnanolone (AlloP), has been shown to synthesize and exert neuroprotective effects on the retina through the $GABA_A$ receptor pathway in a rat model of acute glaucoma *in vitro* (146,147). As a major mitochondrial cholesterol carrier, TSPO mediates the transport of cholesterol into the mitochondria, which is a key process in the synthesis of pregnenolone (57). Pregnenolone then functions as the starting material for AlloP synthesis (83,148). Under elevated pressure (75 mmHg), TSPO expression is found to be upregulated and TSPO colocalizes with AlloP and 5α-reductase (5αRD; a rate-limiting enzyme in the AlloP synthesis pathway) in RGCs, suggesting that RGCs are the principal site of AlloP synthesis (57). Furthermore, the TSPO antagonist, atriol, significantly inhibits the production of AlloP (149), suggesting that TSPO is important in AlloP synthesis. In addition, atriol induces changes in retinal excitotoxicity, including edema-like changes in the inner plexiform layer and bull's eye formation in the inner nuclear layer (150,151). Moreover, the TSPO ligand, PK11195, acts as a selective agonist that promotes TSPO expression and inhibits pressure-induced RGC apoptosis (57). Atriol and 5αRD inhibitors (24) reverse this effect, suggesting that PK11195 may exert neuroprotective effects by promoting the TSPO-5αRD-mediated AlloP synthesis pathway, as aforementioned. Hence, TSPO agonists may have therapeutic potential for ocular hypertension injury.

6. Conclusion

Overall, the present review concluded that TSPO is broadly involved in multiple cellular processes as well as mitochondrial functions. TSPO participates in the occurrence and development of various ocular diseases, including AMD, DR, retinal ischemia and glaucoma, with evidence of both protective and aggravating effects in the observed pathology of the diseases. There is increasing evidence that endogenous or synthetic TSPO ligands, which modulate TSPO functions, play beneficial roles in the aforementioned diseases primarily by promoting steroidogenesis, maintaining cholesterol homeostasis, exerting anti-inflammatory effects, decreasing ROS production and regulating microglial activation. These findings suggest that TSPO may be a key potential therapeutic target. Despite the progress made in understanding the role of TSPO in ocular diseases, the expression of TSPO in ocular surface tissues, the lens, the lacrimal gland and the optic nerve and whether TSPO plays a key role in these diseases remain to be investigated. Moreover, whether TSPO is an essential protein for ocular tissue in healthy individuals is another question that requires more extensive study. At present, the use of TSPO ligands in the ocular environment is limited and there is a lack of comprehensive evaluation of their potential adverse effects. Only by addressing these issues can TSPO and its ligands be applied on a larger scale.

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Authors' contributions

MY and SZ designed the study; MY performed the figure preparation and manuscript draft; and SZ reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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