

# Translocator Protein TSPO (Peripheral Benzodiazepine Receptor): The Modern Story of the Ancient Preserved Protein with Ambiguous Functions

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## Abstract

In several tissues, including the brain, heart, blood, intestines, adrenal glands, and liver, the 18 kDa translocator protein (TSPO) was shown to be the peripheral benzodiazepine receptor. There is a strong evidence that TSPO is expressed in microglial cells in the central nervous system. Five transmembrane regions are seen at the cellular level in TSPO at the contact points between the outer and inner layers of mitochondria. The cytosolic region of the complex of amino acids that binds cholesterol is where cholesterol is taken up. TSPO is found as a monomer of 18 kDa and homomultimers and homodimers. Different factors, such as cholesterol concentration and reactive oxygen species, change the multimeric structure. As a result, TSPO gains responsibility for transferring cholesterol to the mitochondrial intermembrane space, transforming it into a steroid. Additionally, TSPO appears to collaborate with other mitochondrial membrane proteins to play a part in regulating the activity of the MPTP (mitochondrial permeability transition pore) and, therefore, in the elements of apoptosis. In vivo imaging of TSPO addresses a significant test in examining brain pathology like neuroinflammatory, Alzheimer's, and schizophrenia. Additionally, TSPO's use as a biomarker may have important implications for developing more viable diagnostic and therapeutic approaches. The current work surveys the TSPO cellular origin and attempts to comprehend its role in various physiological and pathological conditions.

**Keywords:** Peripheral benzodiazepine receptors, Translocator protein TSPO, Steroidogenic acute regulatory protein StAR, Cholesterol, Mitochondria, Central benzodiazepine receptor CBR.

## البروتين الناقل (مستقبل البنزوديازيبين المحيطي): القصة الحديثة للبروتين القديم المحفوظ بوظائف غامضة

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### الخلاصة

في العديد من الأنسجة، بما في ذلك الدماغ والقلب والدم والأمعاء والغدد الكظرية والكبد، تبين أن البروتين الناقل (TSPO) 18 كيلو دالتون (هو مستقبل البنزوديازيبين المحيطي). هناك دليل قوي على أن TSPO يتم التعبير عنه في الخلايا الدبقية في الجهاز العصبي المركزي. تُرى خمس مناطق عبر الغشاء على المستوى الخلوي في TSPO عند نقاط الاتصال بين الطبقتين الخارجية والداخلية للميتوكوندريا. المنطقة العصارية الخلوية في مجمع الأحماض الأمينية التي تربط الكوليسترول هي المكان الذي يتم فيه امتصاص الكوليسترول. تم العثور على TSPO كمونومر من 18 كيلو دالتون ومولدات متجانسة والأشكال المتعددة. عوامل مختلفة، مثل تركيز الكوليسترول وأنواع الأكسجين التفاعلية، تغير البنية المتعددة. نتيجة لذلك، تكتسب TSPO مسؤولية نقل الكوليسترول إلى المناطق بين الغشاء في الميتوكوندريا، وتحويله إلى الستيرويد. بالإضافة إلى ذلك، يبدو أن TSPO تتعاون مع بروتينات غشاء الميتوكوندريا الأخرى لتلعب دورًا في تنظيم نشاط MPTP مسام انتقال نفاذية الميتوكوندريا وبالتالي في عناصر موت الخلايا المبرمج. يعالج التصوير في الجسم الحي لـ TSPO اختبارًا مهمًا في فحص أمراض الدماغ مثل الالتهاب العصبي ومرض الزهايمر والفصام. بالإضافة إلى ذلك، قد يكون لاستخدام TSPO كمؤشر حيوي لتحسين الاستراتيجيات التشخيصية والعلاجية الأكثر قابلية للتطبيق. يستعرض البحث الحالي أصل TSPO الخلوي ويحاول فهم دوره في مختلف الظروف الفسيولوجية والمرضية. الكلمات المفتاحية: مستقبلات البنزوديازيبين المحيطية PBRs، البروتين الناقل TSPO، البروتين التنظيمي الحاد الستيرويدي StAR، الكوليسترول، الميتوكوندريا، مستقبل البنزوديازيبين المركزي CBR.

## Introduction

### Translocator protein (TSPO)

Translocator protein (TSPO), formerly known as PBR (peripheral benzodiazepine receptor), is a tryptophan-rich sensory protein<sup>(1)</sup> with an estimated molecular weight of 18 kDa<sup>(2)</sup> and encoded by the TSPO gene<sup>(3,4)</sup>. TSPO is present on the external mitochondrial membrane in all human body tissues and the brain<sup>(4)</sup>. It is responsible for transporting cholesterol inside the mitochondria and is proposed to be mediated by the steroidogenic acute regulatory protein (StAR)<sup>(2)</sup>.

### Structural organization of TSPO

TSPO is a protein only found in the outer membrane of mitochondria. It is encoded in the nuclear DNA.<sup>(4,5)</sup>

The peripheral type benzodiazepine and the mitochondrial benzodiazepine receptors were earlier names for TSPO. In 2006, the term "TSPO" was selected based on what was discovered about its molecular structure and functions<sup>(1)</sup>.

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TSPO protein structure has been identified in three dimensions for mammalian and bacterial proteins<sup>(2,6,7)</sup>. The following is a clockwise sequence of the five TMs that makeup TSPO: When seen from the cytosol, the order of the TMs is TM1-TM2-TM5-TM4-TM3, as shown in Fig. 1(A)<sup>(2)</sup>.

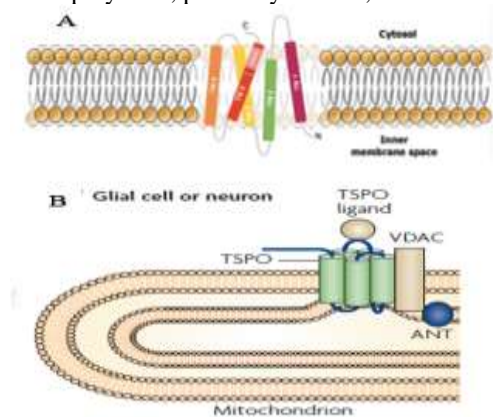
TSPO has been shown to form complexes with various metabolites and peptides, including porphyrins, phospholipase A2, cholesterol, and diazepam-binding inhibitors<sup>(8)</sup>.

The 169 amino acids in TSPO were subjected to hydropathy profile analysis. It predicted a structure with five transmembrane helices, which have now been provisionally verified<sup>(9)</sup>, as shown in Fig.1<sup>(2)</sup> below<sup>(13-15)</sup>

Certain mitochondrial proteins interact with TSPO in particular ways. This fact has led to the idea that TSPO puts together a complex of proteins from the outside and inside of the mitochondrial membranes, such as the ANT (adenine nucleotide transporter) and the VDAC (voltage-dependent anion channel) as in figure 1/B<sup>(10,11,12)</sup>.

Based on these findings, it is thought that TSPO is part of the mitochondrial contacting sites between the external and internal membranes. It helps lipophilic molecules get through the aqueous space between the membranes, as shown in Fig. 1(A, B)<sup>(2,13-15)</sup>.

This hypothesis postulates that when TSPO is formed, it is often confined to specific contact sites<sup>(16)</sup>. Mitochondrial activities, such as through steroid synthesis and cell proliferation, seems to improve TSPO's potential to synthesize homopolymers, primarily trimers, and dimers<sup>(17,18)</sup>.



**Figure 1. A: TSPO topology in the mitochondrial membrane. B: TSPO present in the outer mitochondrial membrane of the mitochondria. It is connected to the inner mitochondrial membrane's VDAC (voltage-dependent anion channel) and ANT (adenine nucleotide transporter).**<sup>(13-15)</sup>

### **Early Peripheral Benzodiazepine receptor PBR to recent Translocator Protein TSPO**

The diazepam binding site was addressed in the rat brain, utilizing [3H]Diazepam, by Braestrup and

Squires, (1977)<sup>(19)</sup>. Further research discovered that clonazepam displaced tritium-labeled diazepam [3H]-diazepam in brain sites with specific binding for [3H]-diazepam. These sites were found to be associated with the plasma membrane fraction<sup>(19)</sup>. Further studies showed [3H]-diazepam binding sites in extra-brain tissues like the liver, kidney, and lungs displaced by the non-GABA<sub>A</sub> benzodiazepine derivative Ro5-4864. These sites were confined with a mitochondrial fraction<sup>(19)</sup>.

These disclosures proved the presence of the peripheral benzodiazepine receptor (PBR), also related to the previous mitochondrial benzodiazepine receptor, or  $\omega_3$  receptor. Moreover, diazepam exhibited an affinity for central benzodiazepine receptors (CBR) or GABA<sub>A</sub> and PBR<sup>(20)</sup>. Several studies have also shown that CBR and PBR have different proteins, tissues, and subcellular locations, which means they have different pharmacology<sup>(21,22,23)</sup>. CBR was confined to neurons and glial cells<sup>(24,25,26)</sup>.

Two ligands have been shown to have a specific affinity for PBR but not CBR: the non-benzodiazepine isoquinoline carboxamide PK11195 and the inactive diazepam derivative 4-chlorodiazepam (Ro5-4864). These two were investigated in the characterization of the brain's PBR. Various studies have shown that the latter is altered during various models of brain injury and neurodegeneration. In animal models of gliosis, for example, it has been shown that the amount of binding for both substances (labeled [3H]-PK11195 and [3H]-Ro5-4864) increases at both the primary and secondary sites of brain injury<sup>(27-35)</sup>.

However, the PBR was first hypothesized to translocate or transport cholesterol for the rate-limiting step in pregnenolone synthesis and the formation of neurosteroids from the internal to the external mitochondrial membrane<sup>(36-39)</sup>.

Thus, the way that the name PBR was utilized makes no sense regarding the classical way of describing neurotransmitter receptors or peripheral localization<sup>(38,39)</sup>.

In 2006, a consensus was reached to clear up this confusion. Based on the molecular weight and predicted activity, the term PBR was modified to 18 kDa TSPO<sup>(37)</sup>.

### **Evolution of TSPO**

The TSPO gene family's function has broadened from environmental sensor to bioregulator<sup>(40)</sup>. For instance, bacterial TSPO serves as an oxygen sensor and controller of photosynthesis<sup>(41)</sup>. The protein sequences of mammalian TSPO and bacterial TSPO are barely 30% similar. However, it can serve as an oxygen sensor in place of bacterial TSPO<sup>(41)</sup>.

In recent years, it has been clear that TSPOs in the non-photosynthetic eubacterium *Pseudomonas fluorescens* are very structural to their

mammalian equivalents in structure and function. The TSPO of the non-photosynthetic eubacterium *Pseudomonas fluorescens* is comparable in structure and function to those of TSPOs in mammals. For example, it has a binding affinity for the prototypical TSPO ligand PK11195<sup>(42)</sup>. Plants and certain archaea populations possess a binding affinity for the prototypical TSPO ligand, PK11195<sup>(42)</sup>. Archaea in certain populations and plants possess TSPO as well<sup>(40)</sup>.

Notwithstanding, a few living organisms, such as *Saccharomyces cerevisiae* and *Escherichia coli*, show an absence of TSPO. In these organisms, TSPO has been supplanted by other proteins, giving rise to the non-fundamentality of TSPO for biological activity<sup>(43)</sup>.

Multiple TSPO genes have been demonstrated in different animals and plants, for instance, Tspo1 and Tspo2<sup>(44)</sup>. The manufactured ligand PK11195 showed a stimulatory effect on cholesterol transport into mitochondria by binding to Tspo2<sup>(7)</sup>.

TSPO polymorphism, specifically the mutation of the Ala 147 residue to Thr, is associated with elevated anxiety<sup>(45)</sup>. This polymorphism exhibited a diminished affinity for cholesterol and PK11195<sup>(6)</sup>.

Likely, a mutated TSPO with a diminished binding affinity of ligands has been proposed in the model of a bacterial TSPO imitating human polymorphism. This may give further perception to the anticipation of human psychiatric disorders with respect to the pathogenic mechanism of TSPO polymorphism. This way, later and ongoing examinations tried to comprehend the pathophysiological relation of TSPO in the brain<sup>(46)</sup>.

### **Function**

Depending on the tissue, the mitochondrial protein TSPO (PBR) located on the external mitochondrial membrane of humans and animals has many putative functions. The most extensively studied of these have been linked to roles in apoptosis, steroid synthesis, and immune response<sup>(47)</sup>.

### **Bile acid biosynthesis and cholesterol transport**

Cholesterol transport through the mitochondrial intermembrane space is primarily connected to TSPO, as previously described, and is necessary for the bile acid and steroid synthesis processes in the associated organs. Pharmacological TSPO ligands promote cholesterol transport, activating the process<sup>(48)</sup>.

TSPO deletion in genetically engineered mouse models has yielded contradictory outcomes regarding the physiological need for TSPO's role in steroidogenesis. This cancellation did not affect Leydig cells' testosterone synthesis<sup>(38)</sup>. On the other hand, pharmacological and biochemical studies have shown TSPO's centrality to cholesterol

transport and steroid production inside cells<sup>(49)</sup>. The significance of this interaction to TSPO is still debatable.

### **Heart Regulation**

In both chronotropic and inotropic effects, it has been shown that voltage-dependent calcium channels and TSPO work together in cardiac myocytes<sup>(50)</sup>. This communication between TSPO and calcium channels was manifested by the change in myocardial action potential duration, hence the heart contractility. As a result, TSPO serves a cardio-protective function in healthy individuals. Conversely, it can be cardio-damaging during infection when it is upregulated due to restriction of the inflammatory reaction<sup>(51)</sup>.

### **Immunomodulation**

TSPOs can affect lymphocytes, macrophages, neutrophils, and mass cells<sup>(50)</sup>. It can hinder the multiplication of lymphocytes, affecting the release of cytokines by macrophages and the balance of oxidative blasts by neutrophils<sup>(52, 53)</sup>.

Upregulation of TSPO expression has also been seen in inflammatory responses after neurodegenerative diseases, hemorrhagic brain injury, ischemia-reperfusion injury, and myocarditis. All of these upregulations cause myocardial necrosis<sup>(54, 55)</sup>.

Another example of expanded TSPO expression has been detected during Coxsackie virus B3 (CVB3) infection. Whereas inflammatory infiltration is mediated by leukocyte adhesion and migration, CD11b+ macrophages are recruited<sup>(51)</sup>.

The upregulated CD11b+ macrophages, following infection, caused an expanded expression of TSPO. Inflammation of the heart muscle (myocardium) develops, which may progress to heart failure after dilated cardiomyopathy<sup>(51)</sup>.

### **Apoptosis**

TSPO ligands were found to decrease mitochondrial transmembrane potential, thus altering the apoptosis of thymocytes in lymphatic tissues. TSPO ligands triggered the death of cancer cells (apoptosis) in human colorectal cancer cells<sup>(56)</sup>.

### **Stress adaptation**

It has been discovered that TSPO, comparable to human and bacterial TSPO, is present in the moss *Physcomitrella patens*, a basal land plant. It was found to be fundamental for accommodating salt stress<sup>(57)</sup>.

### **Tissue distribution**

In addition to CBR at the plasma membrane, PBR is present in the brain but at expression levels about a quarter as high<sup>(58)</sup>. TSPO is found in numerous body areas, including the human iris/ciliary body<sup>(59)</sup>, heart, liver, adrenal, testis, hemopoietic, and lymphatic cells<sup>(60)</sup>.

### Therapeutic implementations

TSPOs have been demonstrated to be engaged with various cycles, for example, inflammation<sup>(61, 62)</sup>, and TSPO ligands might be valuable as anticancer drugs<sup>(63, 64)</sup>.

It has been shown that TSPO ligands like emapunil (XBD-173) or Alpidem can be promoted by the production of allopregnanolone, a neuroactive steroid in the brain that can help reduce anxiety<sup>(66, 67)</sup>. However, toxicity-related adverse effects remain a huge obstruction in the drug development of these drugs<sup>(68)</sup>, which may hold a benefit as anxiolytics with fewer habit-based adverse effects than traditional benzodiazepine-type drugs<sup>(69,70,71,72)</sup>.

In an Alzheimer's disease model in mice, TSPO ligands were found to inhibit or at least partially cure the disease<sup>(68)</sup>.

Regarding the cardiovascular system, studies found that hindering the overproduction of TSPO helped reduce arrhythmias brought about by ischaemia/reperfusion injury<sup>(2)</sup>. Furthermore, TSPO ligands are used to restore the normal action potential of the heart after ischaemia/reperfusion injury<sup>(40)</sup>.

### TSPO as a biomarker

The mammalian (mouse) translocator protein (TSPO) was utilized to identify the first high-resolution 3D solution structure in a complex with its relevant PK11195 ligand using NMR spectroscopy<sup>(2)</sup>. In the presence of its specific ligand, PK11195, mammalian TSPO exists as a monomer (i.e., the mTSPO-PK11195 complex)<sup>(2, 40)</sup>.

Therefore, TSPO is regarded as a noninvasive biomarker for some cardiovascular disorders, like cardiac hypertrophy, myocardial infarction (I/R-injury), atherosclerosis, dysrhythmias, and big vessel vacuity<sup>(55)</sup>. Moreover, TSPO may be a valuable biomarker for detecting atherosclerotic plaque and other inflammatory cardiovascular conditions<sup>(50)</sup>.

Additionally, TSPO ligands were found to be beneficial in neuroimaging, particularly in brain inflammation and reactive gliosis. Also, early clinical trials have shown that TSPO ligands might help treat neurological and mental disorders<sup>(46)</sup>.

### TSPO ligands

#### 1. TSPO Endogenous ligands:

a) TSPO has many important endogenous ligands, including cholesterol and porphyrins. It has TSPO affinities in the nanomolar and micromolar range<sup>(73)</sup>.

b) Endozepines are a group of neuropeptides. They were recognized for their capacity to displace benzodiazepines from TSPO. Diazepam-binding inhibitor (DBI), a common polypeptide precursor

generated by a single gene extensively expressed in the nervous system, is converted into endozepines by endogenous proteolytic processing<sup>(74)</sup>.

The following are the principal physiologically active peptide fragments:

a) ODN (Octadecaneuropeptide Dbi33–50).

b) TTN (Triakontatetrapeptide Dbi17–50)<sup>(75)</sup>.

Both can activate mitochondrial steroid synthesis. There is evidence that DBI has a high affinity for acyl-coenzyme A (acyl-CoA) esters (known as acyl-CoA-binding protein)<sup>(76)</sup>.

c) PAP7 (PBR-associated protein): The binding of TSPO to this protein was observed<sup>(77)</sup>. DBI is a close relative of this protein<sup>(78)</sup>. It is also necessary to operate a signal transduction protein complex in steroidogenic cells that promotes cholesterol import into the mitochondria and is positioned on the external mitochondrial membrane.<sup>(79)</sup>

Specifically, Schwann cells at the periphery of the nervous system are responsible for the production of endozepines. Endozepine synthesis and TSPO expression both increase locally after injury<sup>(80)</sup>.

Glial cells are the primary cell type in which the DBI gene is expressed in the central nervous system<sup>(81)</sup>.

### Synthetic ligands

#### Neuroimaging agents

Many synthetic ligands, including PK11195 and Ro5-4864, originally created as radiolabelled neuroimaging agents, have shown a high affinity for TSPO<sup>(46)</sup>. Three distinct generations of ligands were identified. The 11C-PK11195 is the first-generation ligand. Most TSPO studies use this radiotracer<sup>(82)</sup>. The second-generation tracer, the 11C-DPA-713, was recently developed. In comparison with 11C-PK11195 and other TSPO tracers, it has better in vivo tracer characteristics (increased brain uptake) and greater sensitivity (for example, higher SNR and specific binding) for detecting neuroinflammation in human subjects and rodent models of neurologic disease<sup>(83, 84)</sup>. 11C-PBR28 is another second-generation tracer utilized to treat neurologic illnesses in the clinic, including chronic and dementia pains<sup>(82, 84)</sup>. In PD patients, 11C-PBR28 has been utilized to track immunomodulatory treatments. 11C-PBR28 has a stronger binding to TSPO and a stronger affinity for it than 11C-PK11195<sup>(84)</sup>.

For the rs6971 polymorphism, the 11C-ER176 tracers of the third generation were insensitive. PK11195's quinazoline equivalent was shown to be a potential contender with little sensitivity to the rs6971 polymorphism in vitro<sup>(82, 84)</sup>.

### Agonists

These agents were developed to have anxiolytic effects without the sedative action of benzodiazepines. They change how steroidogenesis is controlled, especially when making neuroactive steroids like allopregnanolone in the brain<sup>(64, 66)</sup>.

The new small-molecule TSPO agonist YL-IPA08 had potent anti-PTSD-like effects in various animal models, with these effects correlating with elevated levels of the hormone allopregnanolone in the brain<sup>(85)</sup>. However, the exact timing of YL-onset IPA08s and the mechanisms behind them are yet unknown.

Etifoxine (Stresam) is a drug used to treat depression and anxiety disorders that have been licensed for use in various countries<sup>(86)</sup>.

- A member of the imidazopyridine medication family, Alpidem (Ananxyl) is an anxiety reliever. It has a connection to the more well-known sleeping aid, zolpidem. On the other hand, Alpidem has a specific function for treating anxiety and, unlike zolpidem, does not have sedative effects at regular dosages<sup>(87, 88)</sup>.

- A selective agonist at the peripheral benzodiazepine receptor, emapunil (AC-5216, XBD-173), is an anti-anxiolytic medication. It is referred to as TSPO, or mitochondrial 18 kDa translocator protein<sup>(65, 89)</sup>.

### Antagonist

a) A selective ligand for the peripheral benzodiazepine receptor, PK-11195, is an isoquinoline carboxamide (PBR). The 18 kDa translocator protein of the mitochondrial, or TSPO, is what it is called. Due to its high affinities for the PBR in all species<sup>(90)</sup>, it is one of the most often utilized PBR ligands, while newer, more specific ligands are beginning to take their place<sup>(91)</sup>.

b) Temazepam<sup>(92)</sup>

c) FGIN-143<sup>(93)</sup>

d) GML-1<sup>(94)</sup>

e) SSR-180,575<sup>(95)</sup>.

### Conflict of Interest

Review introductory article about Peripheral Benzodiceptors "Translocator Protein"

### Funding

No funding "Review article"

### Ethics Statements

Neither animal nor human studies were conducted

### Author Contribution

Single author contribution

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