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Mitochondrial TSPO as a target for metabolic syndrome interventions

Lukasz Kurach*

Independent Laboratory of Behavioral Studies, Medical University of Lublin, Poland

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ABSTRACT

The 18 kDa translocator protein (TSPO) is a protein located in the outer mitochondrial membrane that plays a crucial role in mitochondrial transport, maintaining cellular homeostasis, and ensuring normal cell function. TSPO has beneficial effects in regulating various pathophysiological processes, including the inflammatory response, oxidative stress, steroid synthesis and microglial function. The use of TSPO ligands in different experimental settings has led to their translation to clinical trials for treating neurological and psychiatric diseases. Since TSPO drug ligands influence numerous local processes, such as adipokine secretion, glucose metabolism and adipogenesis, TSPO may represent a promising therapeutic target with potential application for metabolic syndrome. From a clinical perspective, targeting mitochondrial metabolism to modulate energy homeostasis is a promising strategy for developing new antidiabetic or anti-obesity drugs. This review aims to summarize current knowledge of TSPO and its potential as a therapeutic target in metabolic syndrome.

INTRODUCTION

Metabolic syndrome (MetS) is a complex disorder characterized by a cluster of metabolic risk factors that increase the possibility of cardiovascular disease and type 2 diabetes. The diagnosis of MetS has traditionally been based on criteria that vary among different organizations, generally requiring the presence of at least three of the following components: increased waist circumference, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, hypertension and elevated fasting glucose levels. However, considering the advances in understanding the individual components of MetS and the most recent clinical guidelines, a revised definition has been proposed. This updated approach identifies MetS based on the presence of obesity and at least two of the following three criteria: elevated blood pressure, impaired glucose metabolism, or increased non-HDL cholesterol levels (indicative of atherogenic dyslipidemia) [1]. According to the International Diabetes Federation report from 2021, approximately 537 million adults are living with diabetes, and this number will rise to 643 million by 2030 and 783 million by 2045 [2].

The mechanisms of MetS are complex and remain to be fully elucidated. It should be emphasized that environmental and lifestyle factors, such as the consumption of excess calories and lack of physical activity, are the major contributors to MetS. Visceral adiposity has been demonstrated to be a primary trigger for most of the pathways involved in MetS, thus stressing the importance of a high caloric intake as a major causative factor. Among all the proposed mechanisms, insulin resistance, neurohormonal activation and chronic inflammation appear to be the primary drivers of the initiation, progression, and transition of MetS [3]. In particular, adipose tissue dysfunction leads to the dysregulated secretion of adipokines, such as leptin, adiponectin and resistin, as well as pro-inflammatory cytokines like TNF-α and IL-6, which play a central role in perpetuating systemic insulin resistance and vascular inflammation [4].

Along with modifying lifestyle factors, pharmacotherapy is another option for the prevention and progression of MetS. Major pharmacological interventions include the management of dyslipidemia with statins, decreasing prothrombotic risk with antiplatelet drugs and the use of insulin sensitizers to decrease the risk of diabetes. Emerging treatments such as GLP-1 receptor agonists and SGLT2 inhibitors have shown additional cardiovascular and renal benefits in MetS patients, beyond glycemic control, and are increasingly being incorporated into therapeutic strategies [5]. Moreover, agents targeting hepatic lipid metabolism, such as PPARα/γ dual agonists or ACC inhibitors, are under investigation to mitigate hepatic steatosis and atherogenic

* **Corresponding author**
e-mail: lukasz.kurach@umlub.pl

dyslipidemia, which often co-exist in MetS [6,7]. Therefore, as there is no single drug therapy for MetS, the current approach involves polytherapy, which may result in more side effects and make treatment more difficult if the patient has other conditions [8].

The therapeutic complexity of MetS underscores the need for multi-target pharmacological strategies or personalized medicine approaches that can simultaneously address its metabolic, inflammatory and endocrine components. In this context, emerging therapeutic targets – such as mitochondrial proteins, adipose-tissue-specific regulators and metabolites derived from the gut microbiome - are being actively investigated for their potential to offer more integrative and safer treatment options. Among these, the 18 kDa Translocator Protein (TSPO) has recently garnered significant attention both as a promising molecular target for the treatment of a broad range of diseases and as a diagnostic biomarker. This growing interest reflects the urgent need to identify novel pharmacological targets capable of mitigating the risk and progression of MetS.

TSPO PROTEIN CHARACTERISTICS

TSPO, also known as the 'translocator protein' or 'peripheral benzodiazepine receptor' (PBR), is an evolutionarily conserved 18-kDa protein predominantly localized in the outer mitochondrial membrane. Initially identified in peripheral tissues, particularly in the kidney, TSPO was first described in 1977 for its high-affinity binding to diazepam, a classical benzodiazepine. This discovery sparked interest in its role beyond the central nervous system, where classical benzodiazepine receptors were previously thought to be restricted [9]. Structurally, TSPO is a five-transmembrane domain protein that forms complexes with other mitochondrial membrane proteins, including the voltage-dependent anion channel (VDAC) and the adenine nucleotide translocase (ANT), supposedly forming what is often referred to as the 'mitochondrial permeability transition pore (mPTP) complex'. This interaction network positions TSPO as a key regulator of mitochondrial function, mediating critical processes such as mitochondrial membrane potential regulation, apoptosis, and reactive oxygen species (ROS) production in response to cellular stress.

A central and well-studied function of TSPO is its involvement in cholesterol trafficking. Specifically, TSPO is proposed to facilitate the translocation of cholesterol from the outer to the inner mitochondrial membrane, a prerequisite for the biosynthesis of steroid hormones. This process is especially critical in steroidogenic tissues such as the adrenal cortex, gonads and certain glial cells, where TSPO expression is upregulated under both physiological and stress-induced conditions. The cholesterol transported by TSPO is subsequently converted to pregnenolone by the cytochrome P450 side-chain cleavage enzyme (CYP11A1), initiating the steroidogenic cascade [10]. Despite evidence supporting TSPO's role in cholesterol transport, some studies have challenged its indispensability in steroidogenesis by demonstrating that steroidogenic mitochondria lacking TSPO retain their ability to import cholesterol and synthesize steroids, suggesting a more modulatory than obligatory role [11]. TSPO also has a high affinity for porphyrins and has been implicated in the intracellular trafficking of porphyrins and heme, essential processes in heme biosynthesis and iron metabolism [12].

Current research is focused on developing improved TSPO PET radiotracers, understanding the role of TSPO in neurological disease pathogenesis, and exploring TSPO as a therapeutic target, especially in the nervous system [13]. TSPO ligands have shown promise in preclinical and clinical studies (e.g., XBD173, etifoxine) for the treatment of anxiety, cognitive impairment, neuroinflammation and neurodegenerative diseases [14,15]. Etifoxine (Stresam®), a TSPO ligand approved in several countries for the treatment of anxiety disorders, exemplifies the clinical relevance of TSPO modulation. Its efficacy is believed to result from a dual mechanism: direct binding with GABAA receptor and indirect enhancement of GABAergic transmission through stimulation of neurosteroidogenesis, particularly the synthesis of allopregnanolone, a potent endogenous modulator of the GABAA receptor. This indirect mechanism allows for anxiolytic effects without direct receptor binding, which reduces the risk of dependence and tolerance typically associated with benzodiazepines [16,17].

Beyond neuropsychiatric applications, TSPO is also being investigated as a biomarker for neuroinflammation through advanced imaging techniques, such as positron emission tomography (PET). TSPO-targeted radioligands, e.g., [11C] PK11195, [18F]DPA-714 and [11C]PBR28, enable visualization of microglial activation in vivo, offering insights into the spatial and temporal dynamics of neuroinflammatory processes [18].

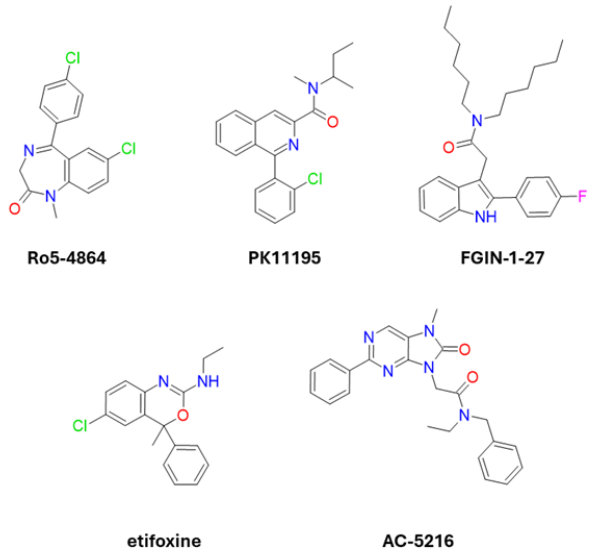

Figure 1. Representative structures of TSPO protein ligands

POTENTIAL OF TSPO IN METABOLIC REGULATION

Despite significant advances in metabolic therapeutics, exemplified by GLP-1/GIP receptor agonists for obesity and type 2 diabetes, identifying novel targets that modulate glucose and lipid metabolism remains a critical research frontier. Among emerging molecular targets, the TSPO protein has recently garnered attention for its multifaceted

role in metabolic homeostasis. TSPO's involvement in energy regulation, lipid transport, adipocyte function and inflammatory signaling positions it as a promising yet underexplored candidate in the context of metabolic disease treatment. Evidence from genetic and pharmacological models underscores TSPO's relevance in glucose and lipid metabolism. Conditional deletion of TSPO in steroidogenic cells in mice leads to pronounced metabolic perturbations, including elevated fasting glucose, increased glycosylated hemoglobin (HbA1c) and elevated free cholesterol, while leaving HDL and triglyceride levels largely unaffected. Notably, these effects exhibit sex specificity, manifesting predominantly in male mice. The dysregulation is accompanied by significant upregulation of S100a8, a pro-inflammatory marker also elevated in the livers of patients with type 2 diabetes, suggesting a potential link between TSPO disruption and hepatic inflammation [19]. In contrast, global germline deletion of TSPO in mice fails to alter basal energy homeostasis, food intake or body composition under both normal and high-fat dietary conditions, hinting at context-dependent and tissue-specific functions of TSPO in metabolic regulation [20].

The role of TSPO in adipose tissue is of particular interest, given the central role of adipocytes in glucose homeostasis and systemic inflammation. TSPO is robustly expressed in both white and brown adipose tissue, where it modulates mitochondrial cholesterol transport and steroidogenesis. In vitro studies using ligands such as PK11195, Ro5-4864, and FGIN-1-27 demonstrate that TSPO activation enhances adipocyte differentiation, upregulates glucose transporter 4 (Glut4) and increases insulin-stimulated glucose uptake. Concurrently, these ligands elevate adiponectin secretion, an anti-diabetic hormone, and suppress the release of pro-inflammatory cytokines such as IL-6. The functional relevance of these findings is reinforced by TSPO knockdown experiments, which impair adipogenesis, attenuate adiponectin production and blunt glucose uptake, thereby mimicking features of insulin resistance [21]. Cholesterol trafficking appears central to TSPO's metabolic effects. The stimulatory actions of TSPO ligands on adipocyte differentiation are inhibited by 3,17,19-androsten-5-triol (19-Atriol), a cholesterol-binding site inhibitor, emphasizing the dependence of these processes on mitochondrial cholesterol shuttling. In liver-specific studies, TSPO deletion results in profound dysregulation of lipid metabolism and inflammation, including altered levels of triglycerides and hepatic cholesterol accumulation. RNA-seq analyses confirm that TSPO deficiency disrupts gene expression pathways involved in lipid homeostasis and fatty acid metabolism [22].

TSPO has also emerged as a regulator of hepatic lipid metabolism and bile acid synthesis in nonalcoholic fatty liver disease (NAFLD). In a study by Li et al., TSPO-deficient hepatocytes exhibited accelerated hepatic steatosis and altered bile acid profiles. This phenotype was mimicked by pharmacological blockade of TSPO's cholesterol-binding site, confirming its functional role in liver lipid homeostasis. These findings position TSPO as a metabolic checkpoint at the intersection of cholesterol handling and bile acid regulation, both dysregulated in diabetes type 2 and obesity [23]. Beyond adipogenesis, TSPO ligands promote the browning of white adipocytes, enhancing mitochondrial biogenesis, thermogenic gene expression, and β-oxidation. These adaptations result in improved systemic lipid metabolism and enhanced insulin sensitivity, highlighting TSPO's therapeutic potential for obesity-related metabolic disorders [21]. In vivo evidence further supports TSPO's metabolic roles. In zebrafish larvae expressing a pck1:Luc2 reporter, TSPO ligands such as Ro5-4864 and PK11195 induce a fasting-like metabolic state characterized by elevated gluconeogenic activity, increased lipid utilization, and decreased whole-body glucose content. These effects persist in hyperglycemic conditions, where PK11195 antagonizes isoprenaline-induced glucose elevation. Transcriptional profiling in both zebrafish and murine models reveals ligand-induced upregulation of genes associated with mitochondrial bioenergetics, gluconeogenesis (e.g., pck1) and fatty acid oxidation, suggesting a conserved metabolic regulatory network mediated by TSPO [24].

In diet-induced obesity models, chronic administration of PK11195 leads to marked improvements in metabolic parameters, including enhanced glucose tolerance, reduced hepatic steatosis and lowered circulating levels of LDL cholesterol and free cholesterol. Additional studies reveal complex, tissue-specific gene expression changes upon TSPO activation, including downregulation of pck1 and srebf1 in liver and upregulation of lipe in adipose tissue, implicating TSPO in both glucose and lipolytic pathways [25]. Moreover, inhibition of TSPO in hypothalamic tanycytes was found to induce lipophagy, thereby increasing local ATP levels and improving whole-body lipid metabolism and energy balance. This central mechanism reveals that TSPO may regulate metabolic processes through CNS-peripheral tissue crosstalk, adding another layer to its systemic role in metabolic diseases [26].

Another promising compound, AC-5216, demonstrates TSPO-dependent antihyperglycemic effects in HFD-STZ rat models of type 2 diabetes. Treatment with AC-5216 normalizes plasma glucose and insulin levels without altering cholesterol or triglycerides. Notably, these effects are blocked by the TSPO antagonist PK11195, confirming the ligand's specificity and TSPO-mediated mechanism of action [27]. Microvascular complications of diabetes are key factors in disease management, from which diabetic retinopathy is one of the most common. Ro5-4864 increased levels of neuroactive steroids like pregnenolone, progesterone and dihydrotestosterone in the sciatic nerve of diabetic rats. This ligand had neuroprotective effects against the pathological changes in peripheral nerves caused by diabetes, likely mediated by the increased neuroactive steroids, which possess neuroprotective properties.

Enhancing TSPO activity to boost indirectly neuroactive steroid levels in nerves and plasma could represent a promising therapeutic approach for diabetic neuropathy. The relevance of TSPO extends beyond metabolic regulation to the mitigation of diabetes-related complications. In rodent models of diabetic neuropathy, Ro5-4864 enhances peripheral neurosteroid synthesis – including pregnenolone, progesterone and dihydrotestosterone – in sciatic nerve tissue, providing neuroprotective effects. Given the well-documented role of neuroactive steroids in modulating neuroinflammation and promoting neuronal survival,

TSPO-mediated enhancement of endogenous steroidogenesis represents a novel therapeutic avenue for managing diabetic neuropathy and retinopathy [28,29].

CONCLUSIONS

TSPO emerges as a pleiotropic regulator of metabolic processes, integrating mitochondrial cholesterol trafficking, neuroactive steroid synthesis, glucose homeostasis, adipocyte differentiation and the modulation of inflammation. Its tissue-specific effects, along with pharmacological evidence across multiple in vitro and in vivo models, highlight its potential as a therapeutic target in metabolic syndrome and associated complications through its multifaceted roles. However, the path to clinical translation remains complex. Discrepancies between pharmacological models underscore the intricacies of TSPO biology, while discovering novel TSPO ligands with high specificity, favorable pharmacokinetics, and minimal off-target effects presents ongoing challenges. This is particularly evident in metabolic diseases, where TSPO's involvement in cholesterol homeostasis, mitochondrial respiration, and inflammation creates both opportunities and obstacles for therapeutic development.

Even with the recent therapeutic successes of GLP-1 receptor agonists – now a cornerstone in treating obesity and type 2 diabetes – the absence of clinically validated TSPO-based treatments for metabolic syndromes highlights the need for deeper mechanistic understanding. Emerging approaches such as structure-based drug design, phenotypic screening in TSPO-overexpressing models, and multi-omics profiling may facilitate the discovery of next-generation TSPO modulators with therapeutic utility beyond the nervous system. As research advances, the TSPO protein may offer a unique entry point for developing multitarget metabolic therapeutics with both endocrine and neuroprotective benefits, warranting comprehensive investigation into its mechanisms and potential clinical applications.

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ORCID iDs

Łukasz Kurach https://orcid.org/0000-0002-1005-8068

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