Biochemical Pharmacology 105 (2016) 1–13

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Research update

Mitochondrial translocator protein (TSPO): From physiology to cardioprotection

Didier Morin[a,b,*], Julien Musman[a,b], Sandrine Pons[a,b], Alain Berdeaux[a,b], Bijan Ghaleh[a,b]

[a] INSERM U955, Équipe 3, Créteil, France
[b] Université Paris-Est, UMR_S955, DHU A-TVB, UPEC, Créteil, France

ARTICLE INFO

Article history:
Received 12 October 2015
Accepted 4 December 2015
Available online 10 December 2015

Keywords:
Translocator protein
Heart
Cardioprotection
Ischemia–reperfusion
Mitochondria

ABSTRACT

The mitochondrial translocator protein (TSPO) is a high affinity cholesterol binding protein which is primarily located in the outer mitochondrial membrane where it has been shown to interact with proteins implicated in mitochondrial permeability transition pore (mPTP) formation. TSPO is found in different species and is expressed at high levels in tissues that synthesize steroids but is also present in other peripheral tissues especially in the heart. TSPO has been involved in the import of cholesterol into mitochondria, a key step in steroidogenesis. This constitutes the main established function of the protein which was recently challenged by genetic studies. TSPO has also been associated directly or indirectly with a wide range of cellular functions such as apoptosis, cell proliferation, differentiation, regulation of mitochondrial function or porphyrin transport.

In the heart the role of TSPO remains undefined but a growing body of evidence suggests that TSPO plays a critical role in regulating physiological cardiac function and that TSPO ligands may represent interesting drugs to protect the heart under pathological conditions.

This article briefly reviews current knowledge regarding TSPO and discusses its role in the cardiovascular system under physiological and pathologic conditions. More particularly, it provides evidence that TSPO can represent an alternative strategy to develop new pharmacological agents to protect the myocardium against ischemia–reperfusion injury.

1. Introduction

Translocator protein (TSPO) was discovered in the 1970s when it was found that some benzodiazepines were able to bind to specific sites in peripheral tissues. These sites were functionally and pharmacologically different from the central benzodiazepine receptors as they were not coupled to gamma-aminobutyric acid receptors [1]. They were located on outer mitochondrial membrane and showed high affinity for ligands that were devoid of activity for central benzodiazepine receptors. They were first denominated PBR for “peripheral benzodiazepine receptors”. The name TSPO was then proposed in 2006 to replace PBR because it was reflecting more accurately its structure and the main potential functions of the receptor, i.e., cholesterol binding and transport, porphyrin binding and transport/import protein [2].

TSPO is a 169 amino acid protein with five transmembrane domains located primarily on outer mitochondrial membranes. TSPO is expressed in a wide variety of species and is ubiquitously distributed with a predominantly expression in steroid-synthesizing tissues [3] such as gonad, adrenal and brain cells but it is also abundantly expressed in kidney and heart. This extensive distribution of the protein and the highly conserved primary sequence of the gene in the evolution suggest an important role for TSPO in biological processes. This idea was reinforced when it was reported that gene-deleted mice displayed an embryonic lethal

Abbreviations: AIF, apoptosis inducing factor; ANT, adenine nucleotide translocase; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; IMAC, inner membrane anion channel; mPTP, mitochondrial permeability transition pore; PBR, peripheral benzodiazepine receptors; RIRR, ROS-induced ROS release; ROS, reactive oxygen species; StAR, steroidogenic acute regulatory protein; TSPO, translocator protein; VDAC, voltage-dependent anion channel.

* Corresponding author at: INSERM U955—Équipe 3, Faculté de Médecine de Créteil, 8, rue Général Sarrail, 94010 Creteil Cedex, France. Fax: +33 1 49 98 36 61.
E-mail addresses: didier.morin@inserm.fr (D. Morin), julien.musman@inserm.fr (J. Musman), s.pons@u-pec.fr (S. Pons), alain.berdeaux@inserm.fr (A. Berdeaux), bijan.ghaleh@inserm.fr (B. Ghaleh).

http://dx.doi.org/10.1016/j.bcp.2015.12.003
0006-2952/

phenotype [4]. However, these data and the model linking the TSPO to the transport of cholesterol from the outer to the inner mitochondrial membrane were recently questioned [5]. Indeed, Selvaraj and co-workers succeeded to generate global TSPO null mice [6] and demonstrated that TSPO would not be essential to steroid hormone biosynthesis [7]. In addition to its potential role in steroid synthesis, as a component of the outer mitochondrial membrane, TSPO was involved in the regulation of other mitochondrial functions such as regulation of respiration, of the membrane potential or opening of the permeability transition pore (mPTP) [8]. Several biological processes such as apoptosis, cell proliferation, modulation of voltage dependent channels or microglial activation related to brain damage are also regulated, at least partly, by TSPO [9,10]. However, some of these effects were evidenced by means of TSPO ligands and further experiments are necessary to conclude in confidence that these effects reflect a direct involvement of TSPO.

In the heart, the role of TSPO remains elusive. In the recent years, a growing body of evidence suggests that TSPO and its ligands could play a protective role during cellular stress. TSPO has been involved in the reduction of infarct size in several models of ischemia–reperfusion, in the prevention of reperfusion arrhythmias, but also in the prevention of cardiac hypertrophy that is a natural course of myocardial infarction [10–14].

The aim of this review is first to summarize what is known about the molecular structure, distribution and hypothetical function(s) of TSPO under physiological conditions with a major focus on the heart. Then, we will review the mechanism(s) that can explain how TSPO ligands can protect the heart against the deleterious effects of ischemia–reperfusion.

2. Pharmacological characterization of TSPO

TSPO was originally described in 1977 by Braestrup and Squires who observed the presence of high density binding sites for radiolabeled diazepam in the kidney [15]. Then, these sites were found in other tissues including the central nervous system and were named “peripheral benzodiazepine receptors” to distinguish them from the central benzodiazepine receptors and because they were abundant in the peripheral tissues.

In order to study these sites, considerable efforts were made to develop specific and selective high affinity TSPO ligands structurally different from “classical” benzodiazepine molecules. They can be divided in different chemical classes including isoquinoline carboxamides (PK11195) [16], indoleacetamides (SSR180575; FGIN-1-27) [17,18], phenoxyphenyl-acetamides (DAA1106) [18] and pyrazolopyrimidines (DPA-713) [3,18] derivatives. Recently, an acetamide derivative, YL-IPA08 [19] and a molecule structurally close to cholesterol, TRO40303, were found to be novel specific TSPO ligands, the latter recognizing specifically the cholesterol site of the translocator [20] (Fig. 1).

The most used of these ligands to probe TSPO and to investigate its biological role(s) are 4′-chlorodiazepam [15] and the isoquilonine carboxamide derivative PK11195 [16] which display nanomolar affinity for TSPO. Based on thermodynamic properties, 4′-chlorodiazepam was first considered as an agonist and PK11195 as an antagonist of TSPO [21] but different studies demonstrated that this classification is artificial as both ligands can act on the same way or can have opposite effect, depending of the biologic process and/or of the cell. Thus other authors qualified PK11195 and 4′-chlorodiazepam as agonist and antagonist, respectively [10,22].

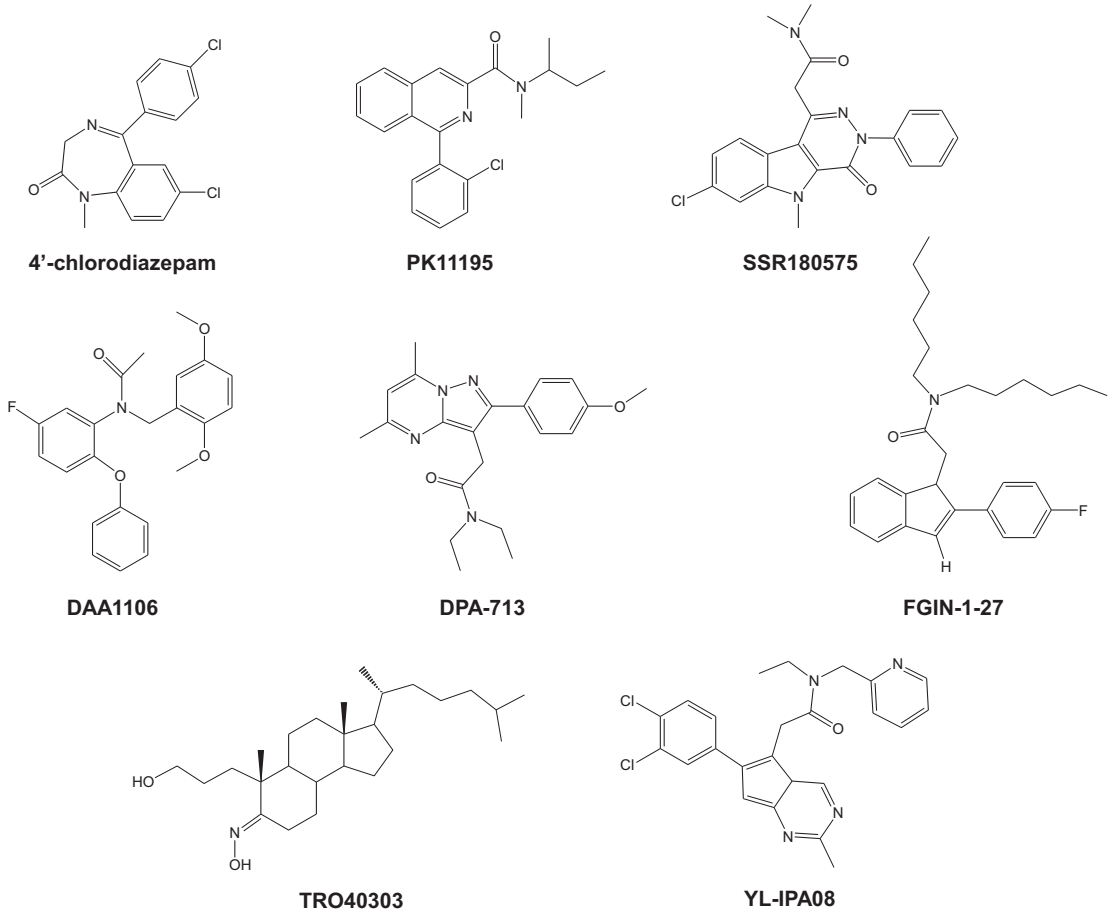

Fig. 1. Chemical structures of TSPO ligands.