Send Orders for Reprints to reprints@benthamscience.ae

168 *Current Aging Science,* **2014,** *7,* **168-175**

Translocator Protein (TSPO) Role in Aging and Alzheimer's Disease

Jayanthi Repalli*

NYU Langone Medical Center, 180 Varick Street, Room 802, New York, NY, 10014, USA

Abstract: Cellular damage and deregulated apoptotic cell death lead to functional impairment, and a main consequence of these events is aging. Cellular damage is initiated by different stress/risk factors such as oxidative stress, inflammation, and heavy metals. These stress/risk factors affect the cellular homeostasis by altering methylation status of several aging and Alzheimer's disease associated genes; these effects can be manifested immediately after exposure to stress and at later stages of life. However, when cellular damage exceeds certain threshold levels apoptosis is initiated. This review discusses the stress factors involved in cellular damage and the role and potential of TSPO-mediated cell death in aging as well as in Alzheimer's disease, which is also characterized by extensive cell death. Mitochondrial-mediated apoptotic death through the release of cytochrome c is regulated by TSPO, and increased expression of this protein is observed in both elderly people and in patients with Alzheimer's disease. TSPO forms and mediates opening of the mitochondrial membrane pore, mPTP and oxidizes cardiolipin, and these events lead to the leakage of apoptotic death mediators, such as cytochrome c, resulting in cell death. However, TSPO has many proposed functions and can also increase steroid synthesis, which leads to inhibition of inflammation and inhibition of the release of apoptotic factors, thereby decreasing cell damage and promoting cell survival. Thus, TSPO mediates apoptosis and decreases the cell damage, which in turn dictates the process of aging as well as the functionality of organs such as the brain. TSPO modulation with ligands in the Alzheimer's disease mouse model showed improvement in behavioral symptoms, and studies in Drosophila species showed increased cell survival and prolonged lifespan in flies after TSPO inhibition. These data suggest that since effects/signs of stress can manifest at any time, prevention through change in lifestyle and TSPO modulation could be potential strategies for altering both the aging process and the progression of Alzheimer's disease.

Keywords: Aging, Alzheimer's disease, apoptosis, mitochondria, neurodegenerative diseases, TSPO.

INTRODUCTION

Aging is a multifactorial genetic phenomenon manifested by slow functional breakdown of tissues and organs due to deleterious changes in the cellular environment throughout life. Changes from exposure to toxins or other stress/risk factors cause cellular damage and after a certain threshold it leads to apoptosis. Thus in healthy human beings, apoptosis works as a sentinel mechanism to destroy damaged cells resulting from inflammation, heavy metals, and reactive oxygen species (ROS), thereby maintaining tissue homeostasis. However, excessive cellular damage and deregulated apoptosis has been linked to age-related pathologies and specifically neurodegenerative diseases [1-8]. TSPO expression is increased in aging people and in patients with Alzheimer's disease (AD) and has been implicated as a modulator of inflammation and apoptosis. This review will start by explaining some of the factors associated with cellular damage and their link to apoptosis and neurodegenerative diseases, and also illustrates the role of Translocator Protein (TSPO).

CELLULAR DAMAGE AND APOPTOSIS-AGING/AD

Cellular damage and apoptosis can be caused by several stress factors such as oxidative stress, inflammation, dietary factors and heavy metals, so having resistance to these can prevent damage and cell death, and can improve organ functionality resulting in an increased life span [6, 7, 9]. Oxidative stress is caused when reactive oxygen species (ROS) such as superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl (OH^-) anions are generated excessively in the cell and are not removed by antioxidant enzymes. Mitochondria are major sources of ROS as they consume most of the available (O_2) to produce adenosine triphosphate (ATP). Superoxide dismutases (SODs) convert O_2^- into H_2O_2, and glutathione peroxidase (Gpx1) and peroxiredoxin (Prx) convert H_2O_2 into water (H_2O) [10]. These ROS react with other cellular components such as membranes, enzymes, proteins, and deoxyribonucleic acid (DNA) leading to disruption of cellular homeostasis, and cell death. Enhanced cell death leads to organ failure, accelerates the aging process and ultimately affects the life span [7, 11]. Aged skeletal muscle volume loss can be attributed to apoptosis as it shows more apoptotic markers such as apoptotic protease activating factor-1 (Apaf-1), caspase 9 and 3 [12]. Extended life span is observed in several animal species that have less ROS compared to animals with more ROS. For example, rats, a species that has naturally high levels of ROS have shorter life spans than pigeons that have less ROS. Furthermore, the deletion of oxidative factors such as p66shc, which is involved in the conversion of O_2 to H_2O_2 in mouse embryonic fibroblasts (MEFs) and mouse models, increased resistance to oxidative

*Address correspondence to this author at the NYU Langone Medical Center,180 Varick Street, Room 802, New York, NY, 10014, USA; Tel/Fax:12122635599; E-mail: jrepalli@gmail.com

1874-6128/14 $58.00+.00

stress, and prolonged cell survival and life span. The ROS induce mutations in DNA, and the correlations between mutations and aging, life span, and neurodegenerative diseases have been observed in several cell culture and animal studies. Studies on skeletal muscle of mice showed that 9-month-old mice that have mitochondrial DNA mutations exhibited increased apoptosis compared to normal mice [7]. Additionally, AD patients showed increased levels of 8-oxodeoxyguanine (8-oxodG), indicating possible oxidative damage, and its induced aberrant methylation might be a causative factor for disease progression [13, 14]. Oxidative stress can be reduced by restricting diet, which enhances stress resistance to ROS. This is corroborated in studies with Caenorhabditis elegans, Drosophila melanogaster, and mice, which all showed a correlation between restricted calorie intake and increased lifespan. Additionally, reduction of insulin/insulin-like growth factor-1 (IGF-1) signaling through knockdown of various genes such as daf-2 and age-1 increased cell resistance and life span in worms, flies and other animals [7].

Cell death is the major contributor for neurodegenerative diseases; however, this phenomenon appears in the late stages of disease. Cellular damage and cellular death can be results of acute exposure or earlier exposure to several kinds of toxins and other stress/risk factors. Some of the risk factors associated with AD are aging, oxidative stress, heavy metals (lead-Pb), vitamin B deficiency, dietary cholesterol, lack of exercise, head trauma, genetics (APOEε4 genotype), and inflammation [8, 13, 15, 16]. According to the LEARn model, early exposure to the above-mentioned factors can cause increase in AD-associated genes such as amyloid precursor protein (APP) and beta secretase/beta-site APP cleaving enzyme (BACE) through increased transcription by transcription factor specificity protein 1 (SP1). Amylod beta (Aβ) is produced from APP *via* the amyloidogenic pathway where it is cleaved by beta and gamma secretases. Increased transcription elevates the levels of Aβ, but it's not enough to manifest pathological symptoms at that time, and these changes are temporary as the levels returns to normal. However, the changes are maintained epigenetically and make the individuals more susceptible to AD development as they age and are exposed to other triggering factors such as oxidative stress and heavy metals. Studies on mice and Cyanomolgus monkeys with Pb exposure support the above phenomenon. The mice/monkeys that are exposed to Pb at early and later stages showed elevated Aβ compared to animals that are exposed only in later stages. As explained earlier, oxidative stress-induced DNA damage is one of the triggering factors for developing AD. For example, oxidative stress-induced 8-oxodG has been proposed to play a role in AD as it leads to the inhibition of methylation leading to elevated levels of AD genes APP, BACE and Aβ [9, 13, 15]. Elevated levels of 8-oxodG are observed in aging people and AD patients [13, 14], so inhibition of oxidative stress might be beneficial. Such inhibition is accomplished through antioxidants such as melatonin as its administration decreased oxidative stress and Aβ in different disease mouse models [15]. Aβ aggregate levels can also be elevated due to the lack of an efficient chaperone system (heat shock protein 70 - HSP70) that removes aggregated/misfolded proteins [17]. Another key factor is inflammation, which is also considered a risk factor for AD; inflammation can be developed as early as during gestation through exposure to toxins, and during different developmental stages, illness, or injury [18]. Elevated levels of cytokines and microglial activations are also observed in the AD patients, and the aging population also has elevated levels of pro-inflammatory factors, including pro-inflammatory cytokines, such as interleukin6 (IL6), and prolonged inflammation causes damage to neurons [18-20]. Vitamin B12/folate deficiency has been documented as one of the stress/risk factors for AD as well as it increases BACE levels, gamma-secretases and Aβ levels through demethylation which occurs when S-adenosylhomocysteine (SAM) levels are reduced. SAM is produced from methionine, which is produced from homocysteine (HCY) in the presence of vitamin B12 and folate [15]. These observations indicate that modification of lifestyle by increasing the antioxidant intake, exercise and avoiding exposure to heavy metals modify the aging and disease progression [9, 13, 15, 18, 19].

THE MECHANISM OF APOPTOSIS

Apoptosis is executed through two regulated pathways: extrinsic and intrinsic. The extrinsic pathway is mediated through transmembrane death receptors, tumor necrosis factor receptor 1 (TNFR1), death receptors 4 and 5 (DR4 and DR5), and Fas, which are activated by proapoptotic ligands, such as TNF, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL). These receptors activate caspases 3, 6, 7, and 8, which then initiate cell death [21]. The intrinsic pathway is carried out in mitochondria and involves the release of cytochrome c (Cyt c), leading to cell death [2]. Mitochondrial-mediated cell death can be increased due to aging [22-24], neurodegenerative diseases [22, 24, 25], DNA damage [26], or the presence of reactive oxygen species (ROS) [27-30]. Mitochondrial-mediated cell death is regulated through TSPO that releases Cyt c from mitochondria through the membrane permeability transition pore (mPTP) formation and cardiolipin (CL) oxidation [30, 31]. Cyt c forms an apoptosome upon binding with Apaf-1 and procaspase 9. The formation of the apoptosome complex is essential for cell death [1, 32]. Additionally, the cleaved caspase 9 molecules from this complex activate executioner caspases 3 and 7, which, in turn, deactivate cell survival mechanisms through inhibition and activation of different enzymes, ultimately leading to apoptosis (Fig. **1**) [1-3, 32-37].

TSPO REGULATES APOPTOSIS

TSPO, an 18 kDa translocator protein, is involved in calcium^{2+} (Ca^{2+}) signaling cascades, steroidogenesis, and cell survival and death, thereby helping maintain homeostasis in the cell [30, 31, 38, 39]. TSPO is present in many different tissues and organs, including steroidogenic tissues, adrenal tissues, ovaries, testes, liver, kidney and brain [38, 40, 41]. TSPO is activated by high Ca^{2+} and ROS generation that occurs at an increased rate in the aging population and in people with AD. Activated TSPO mediates the formation of mPTPs, ROS generation, and CL oxidation, causing the release of Cyt c and, ultimately, cell death [23, 24, 29-31, 39, 42, 43]. TSPO is also involved in the synthesis of neurosteroids. TSPO ligands have been reported to increase neuros-

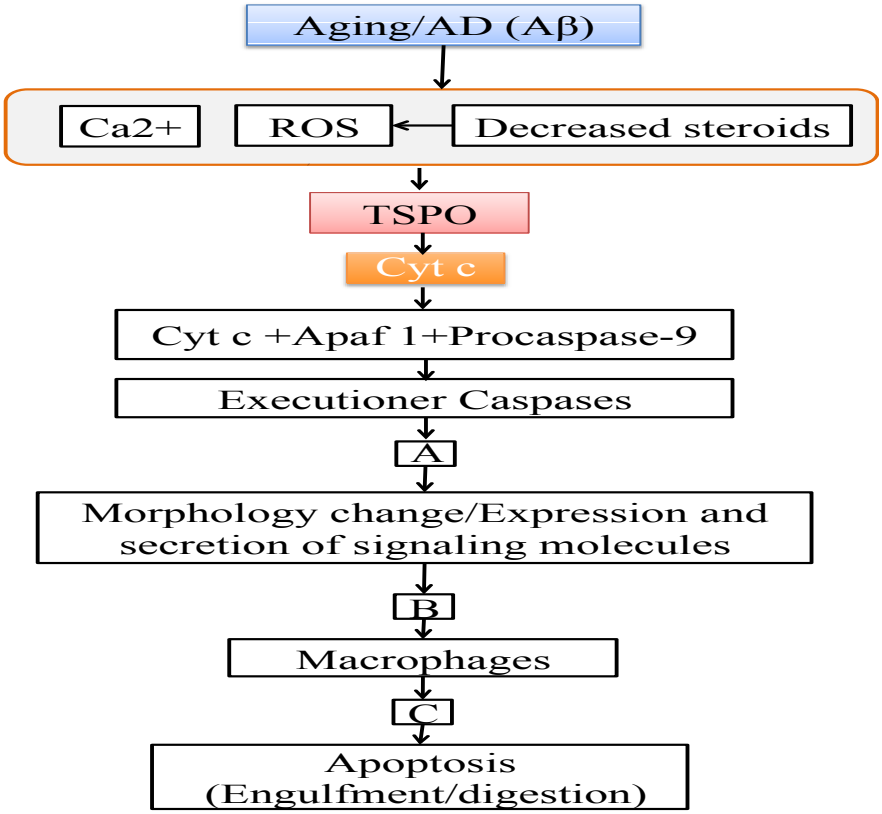

Fig. (1). Schematic representation of steps involved in apoptosis. Aging and AD disturbs the Ca^{2+} homeostasis, increases ROS and decreases neurosteroids and the release of Cyt c through TSPO, which then activates caspases. (**A**) Caspases inhibits several substrates such as poly (ADP-ribose) polymerase (PARP), protein kinase Cδ, retinoblastoma, and degrades lamin leading to inhibition of DNA repair, inhibition of cell cycle progression and nuclear condensation. Activates several other substrates such as gelsolin, MEK kinase 1 (MEKK1) leading to F-actin depolymerization, DNA fragmentation, cytoskeleton organization and plasma membrane blebbing. (**B**) These actions leading to morphological changes and expression/excretion of different signaling molecules such as fractaline, lysophosphatidylcholine (LPC), sphingosine-1-phosphate (SIP), adenosine triphosphate (ATP)/uridine triphosphate (UTP). These molecules recruit macrophages by binding to receptors on the macrophages CX3CR1, G-protein-coupled receptors G2A, SIP-R1/5, P2Y2. (**C**) Recruited phagocytes recognize molecules expressed on apoptotic cells such as thrombospondin, complement C1q, intracellular adhesion molecule 3 (ICAM3), phospholipid phosphatidylserine (PtdSer). Then phagocytes bind them through their receptors cluster of differentiation 36 (CD36), low density lipoprotein receptor related protein 1 (LRP 1), cluster of differentiation 14 (CD14), Tyro-3-Axl-Mer family of receptors (TAM receptors).
Then the cells are then engulfed and digested them by the phagocytes. Alzheimer's disease (AD), amyloid beta (Aβ), apoptotic protease activating factor 1 (Apaf 1), calcium^{2+} (Ca^{2+}), cytochrome c (Cyt c), membrane permeability transition pore (mPTP), reactive oxygen species (ROS), translocator protein (TSPO).

teroid synthesis and inhibit neurodegeneration, and have also shown improved behavioral symptoms in mice, including decreased anxiety and increased cognition. Decreased levels of some neurosteroids are observed in both AD patients and aging people [31, 39, 44-47].

TSPO-mPTP

TSPO regulates the mPTP formation as well as its opening, and it is proposed that TSPO forms mPTP through interaction with the outer membrane voltage-dependent anion channels (VDACs), which transport anions, and the inner membrane channel ATP-ADP translocase (ANT)/cyclophilin D (CypD). The ANT channel transports ADP-ATP, and CypD matrix proteins bind to ANT. mPTP permits the passage of not only calcium but also any other solute below the pore size, which under normal conditions is strictly mediated by specialized channels. This uncontrolled influx of solutes leads to breakage of the outer membrane and the release Cyt c due to inner membrane swelling (Fig. **2**) [30, 31, 38, 39, 42, 48, 49].

TSPO-CARDIOLIPIN OXIDATION

TSPO oxidizes cardiolipin through ROS generation; oxidized lipid no longer binds to Cyt c, resulting in the release of Cyt c into the cytosol through pores formed by TSPO and VDAC (Fig. **2**). Additionally, cardiolipin oxidation enhances the mPTP opening [23, 24, 29, 30, 43].

TSPO-NEUROSTEROIDOGENESIS

One function of TSPO is to transport cholesterol into mitochondria from the cytosol through the transduceosome. Cholesterol gets converted into pregnenolone and then into steroids once it exits the mitochondria. Peripheral-type benzodiazepine receptor-associated protein 7 (PAP7) signal transporter from the golgi apparatus initiates the steroidogenesis by binding to TSPO/VDAC, and by activating

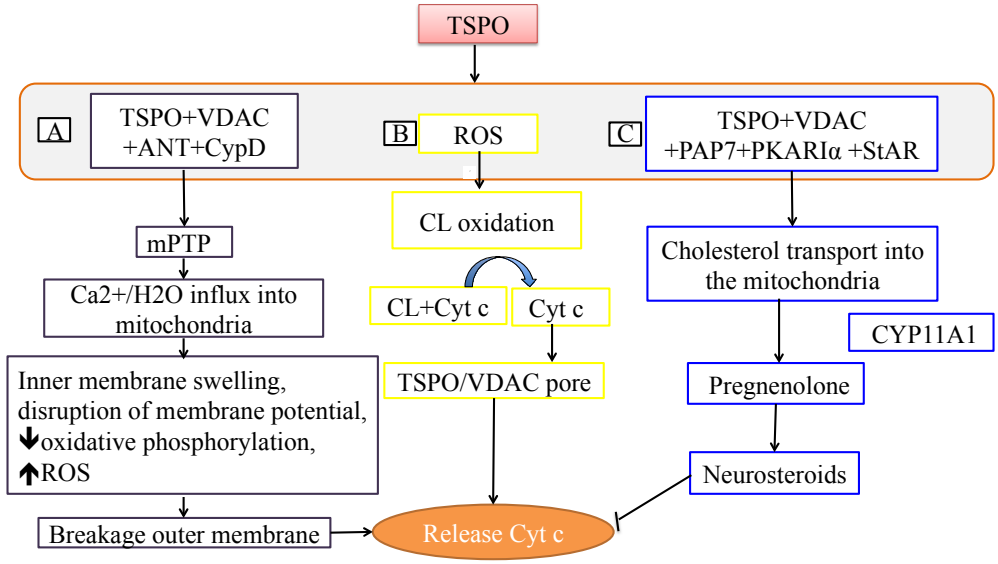

Fig. (2). Mechanisms involved in release of cytochrome c. A) Release of Cyt c through mPTP: TSPO forms a pore with VDAC, ANT and CypD and releases Cyt c. B) Release of Cyt c through CL oxidation: TSPO oxidizes cardiolipin through ROS, that causes dissociation of Cyt c, which is then released through the TSPO and VDAC pore. C) TSPO Neurosteroidogenesis: TSPO increases neurosteroidgenesis by transporting cholesterol into the mitochondria. Increased neurosteroids inhibits release of Cyt c. ATP-ADP translocase (ANT), calcium^{2+} (Ca^{2+}), cardiolipin (CL), cyclophilin D (CypD), cytochrome c (Cyt c), cytochrome P450 enzyme CYP11A1 (CYP11A1), membrane permeability transition pore (mPTP), peripheral-type benzodiazepine receptor (PBR)-associated protein 7 (PAP7), protein kinase A (PKA), PKA-RIalpha (PKARIα), reactive oxygen species (ROS), steroidogenic acute regulatory protein (StAR), translocator protein (TSPO), voltage-dependent anion channels (VDAC), water (H_2O).

protein kinase A (PKA) to form homodimer PKARIα in the presence of excessive cAMP (cyclic adenosine monophosphate). PKARIα phosphorylates steroidogenic acute regulatory protein (StAR), which then delivers free cholesterol to the TSPO complex. StAR also mobilizes the TSPO-bound cholesterol for transport into the mitochondria [39, 50-53]. Neurosteroids can exhibit neuroprotective effects and inhibit cell death by several mechanisms such as inhibition of Ca^{2+} elevation and Cyt c release (Fig. **2**) [31, 38, 39, 44-46]. Additionally, neurosteroids can inhibit the neuroinflammation through inhibiting the release of proinflammatory factors such as cytokines [45].

TSPO MEDIATED APOPTOSIS INFLUENCE ON AGING AND NEURODEGENERATIVE DISEASES

Normal brain tissue contains TSPO in the olfactory bulb, the choroid plexus, and the glial cells at low levels. Aging and neurodegenerative brains, such as brains from patients with AD and Parkinson's disease showed an increased expression of TSPO [31, 38, 54-56], indicating it as a potential culprit for increased apoptosis. AD patients have dementia caused by neuronal dysfunction/loss due to beta amyloid plaques and neurofibrillary tangles and inflammation.

TSPO-MEDIATED APOPTOSIS INFLUENCE ON AGING

Since TSPO mediates apoptosis, its inhibition leads to prolonged cell survival and may improve some of the functions related to cell loss in the aging process. The role of TSPO in cell death and aging was examined by Lin *et al.*, in Drosophila. Drosophila 3rd-instar larval tissues were exposed to gamma-rays at 30 Gray to induce apoptosis and after 3 hours, wing disc cells from TSPO-inactivated (TSPO-/-) and TSPO-knockdown flies showed less apoptosis compared to TSPO wild-type flies. Similarly, cells isolated from 3rd-instar TSPO-/- larval brains exposed to H_2O_2, which induces oxidative stress, demonstrated significant suppression of apoptosis when compared to TSPO wild-type cells from male and female flies, indicating that TSPO plays a key role in the induction of apoptosis. Furthermore, the authors studied the effect of TSPO deletion or TSPO knockdown on the life span of the fly. Interestingly, increased life span was observed only in male TSPO-/- or TSPO knockdown or TSPO depletion Drosophila flies. When these flies were exposed to stress, such as H_2O_2, male TSPO-/- flies had longer lifespans than wild-type flies, while no differences were found between the groups in female flies. Additionally, it was found that TSPO ligands, PK11195 (at moderate concentrations) and Ro5-4864, inhibited TSPO and increased the lifespan in male flies [57].

TSPO IN NEURODEGENERATIVE DISEASES

In positron emission tomography (PET) studies, adult human brains showed increased uptake of the ^{11}C-[R]-PK11195 ligand, which specifically binds to TSPO, when compared to the brains of children [54]. PK11195 can be used as an imaging agent by labeling it to map the inflamed areas of brain. It also exhibits agonistic and antagonistic actions based on its concentration, the cell type, and the environment [58-60]. Brains of patients with neurodegenerative diseases such as AD also showed increased uptake of another ligand, [^{11}C]vinpocetine, in diseased regions, thus, TSPO may also be used as a target to inhibit AD [55].

A reduction of TSPO in the brains of Drosophila flies expressing beta amyloid 42 (Aβ42), a biomarker for AD,

caused a restoration from shortened life span to a normal lifespan in the flies due to decreased caspase 3 and 7 activity and decreased apoptosis [57]. In studies by Barron *et al*., improvements in AD symptoms were observed in the 3xTgAD mouse model of AD when treated with R05-4864, which binds with high affinity to TSPO [44]. R05-4864 can have both apoptotic and antiapoptotic effects depending on its concentration and the context (type of cells) [39, 60]. In this case, treatment-induced Aβ42 clearance and decreased inflammatory markers involved in microglial and astrocyte activity were observed, including ionized calcium-binding adaptor molecule-1 (Iba1) or glial fibrillary acidic protein (GFAP), indicating decreased inflammation. Furthermore, the levels of steroidal hormones such as testosterone and progesterone were increased with the treatment. It can be speculated that these steroidal hormones and inhibition of inflammation are mediating the beneficial anxiolytic and cognitive effects [31, 44]. These cumulative actions mediated by TSPO can positively effect neuronal survival. However, the 3xTgAD mouse model does not show significant cell loss, so further studies in different cell culture and AD mouse models need to be conducted to determine the effect on survival [61]. Additionally, neurosteroids can inhibit inflammation and cell death, which has been shown in several studies and described in reference [45]. Translational relevance of these studies can be highlighted by increased behavioral alertness, including improved attention and memory as well as decreased anxiety, measured through elevated plus maze and Y maze tests [44]. Several studies have documented elevated expression of TSPO in activated microglia, and TSPO ligand PK11195, can inhibit inflammation by decreasing microglial activation and the release of proinflammatory factors such as cytokines, as well as inhibiting apoptosis [62, 63]. Studies by Bin *et al*., revealed that inflamed microglia with TSPO combined with inflamed astrocytes without TSPO is a marker of neuronal loss and irreversible damage. Whereas microglia with low TSPO combined with inflamed astrocytes with high TSPO is a marker of reversible neuron injury [64]. However, further studies are needed to delineate the consequences of expression levels on neuronal survival and death. These results indicate that either modulating or inhibiting TSPO can provide an anti-inflammatory/antiapoptotic effect and improve some functional aspects of brain. However, as explained before, aging and neurodegenerative diseases are the combination of genetics, diet, and environmental factors, so combinations with other interventions can be useful to modulate the process and is discussed in the summary.

SUMMARY

Aging is a systematic deterioration of the human body due to cell death and cell damage caused by exposure to several stress/risk factors throughout life, and it drastically affects the quality of life. Additionally, in neurodegenerative diseases, brain deterioration patterns are similar to aging pathology, so limiting the risk factors through early intervention and inhibition/modulation of apoptosis can potentially prevent/delay aging and/or neurodegenerative diseases. Some of the risks for developing disease can be mitigated by modifying life style, such as restricting calorie intake, preventing exposure to heavy metals, and supplementing with antioxidant agents might inhibit oxidative stress and correct methylation, thereby delaying the aging process and altering/preventing the course of neurodegenerative disease. Modulation/Inhibition of cell death can be a useful tool to slow down the aging process and the progression of neurodegenerative diseases, and TSPO appears to be a promising target (Fig. **3**). Several small molecules that affect neurological disorders have been described in references [38, 60]. TSPO is present in the mitochondrial membrane and functions by forming mPTPs and oxidizing cardiolipin, thereby

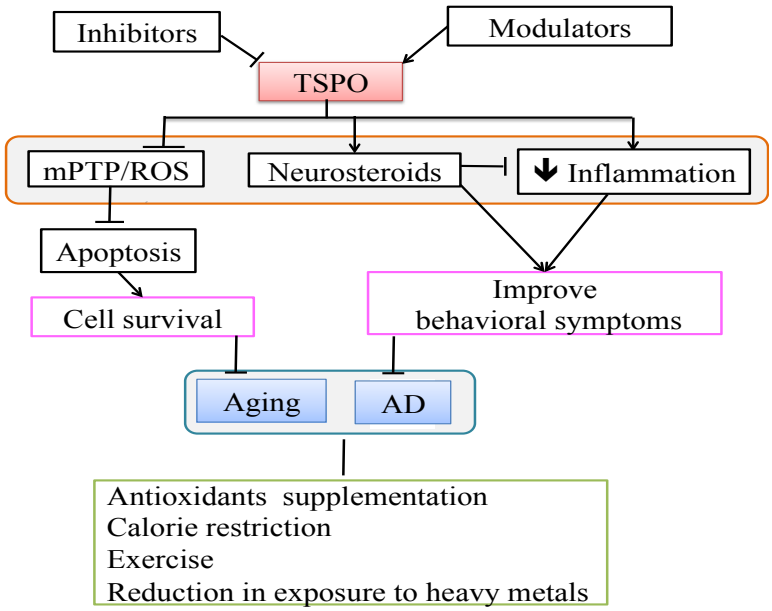

Fig. (3). TSPO as a potential drug target: TSPO inhibition can delay the aging progression through inhibition of apoptosis, and its modulation can delay AD disease by decreasing inflammation and increasing neurosteroids. Antioxidant supplementation, calorie restriction, exercise and reduction in exposure to heavy metals delay aging/AD. Alzheimer's disease (AD), membrane permeability transition pore (mPTP), reactive oxygen species (ROS), translocator protein (TSPO).

regulating Cyt c release. In addition TSPO is involved in the neurosteroid synthesis, which can inhibit inflammation and decrease Ca^{2+} elevation, Cyt c release, and cell death. In aging and neurodegenerative diseases, permeability and cardiolipin oxidation is augmented, possibly due to overexpression of TSPO, leading to increased TSPO-mediated apoptosis. These observations indicate that TSPO is inducing apoptosis of damaged cells. However, this may not be beneficial in this case as it leads to excessive loss of neuronal cells and thereby to the functional decline and decreased life span of the affected individuals. Experiments by Lin *et al*., have provided encouraging results showing an increased cell survival rate and increased life span in Drosophila flies, and Barron *et al*., have observed decreased inflammation, as well as improved behavioral symptoms, in AD mouse models by inhibition and modulation of TSPO. It could be speculated that inhibition of inflammation/apoptosis may help cells regain homeostasis and perform some of the cell loss related functions, so it is important to evaluate the mechanisms of the TSPO ligands with appropriate controls, and also study the effects on the entire organism.

TSPO ligands are used for wide variety of applications such as neuroimaging agents, psychiatric disorders, brain tumors, neuroinflammation, brain damage, and peripheral nervous system lesions [38]. PK11195 and Ro5-4864 are considered to be prototype compounds and several classes of compounds have been developed such as benzodiazepine derivatives, aryloxyanilide derivatives and isoquinoline carboxamide derivatives [65]. Considerations that are applied to develop imaging agents that target TSPO should also be applied to developing TSPO ligands [66]. The molecules that target TSPO should enter the brain and must show optimal retention, affinity and selectivity towards TSPO with safe pharmakokinetics profile with minimal side effects. Based on the ligand affinity, the action of the compounds and their effect on TSPO would change, so careful delineation of particular ligand binding affinity and site, as well as any conformational changes of the protein need to be elucidated to decrease the toxicity and increase the specificity of the compounds before applying them in the clinical setting. Some ligands such as Alpidem showed liver toxicity, so future compounds must be developed to minimize these side effects. TSPO expression is observed in normal neuronal tissues, so the effects of acute administration and long-term administration can be studied [38]. Inhibition and modulation of TSPO can lead to unexpected effects in the organism as it involved in multiple signaling pathways, so careful studies in different control systems should be performed to learn the effect on the entire system. Even though studies are present on both healthy and diseased brain, more studies on TSPO expression and differences in mechanism of action with inclusion of other factors in healthy and diseased brains are still needed in order to increase the potential of developing a successful drug. Since TSPO ligands can be used to affect different pathways in different stages of disease, it may be possible to use them in combination with other agents for neurodegenerative diseases, which have multiple etiologies. As explained above, aging and AD are complex processes with involvement of multiple causative factors, so the combination of different strategies needs to be applied. Based on evidence from published studies, we can conclude that early prevention with lifestyle changes and TSPO can be used as a potential target to inhibit or modulate cellular damage/apoptosis, thereby slowing the aging process, as well as the progression of neurodegenerative diseases.

LIST OF ABBREVIATIONS

8-oxodG	=	8-oxodeoxyguanine
Aβ	=	Amyloid beta
AD	=	Alzheimer's disease
ANT	=	ATP-ADP translocase
Apaf-1	=	Apoptotic protease activating factor-1
APP	=	Amyloid precursor protein
ATP	=	Adenosine triphosphate
BACE	=	Beta-site APP cleaving enzyme
Ca^{2+}	=	Calcium^{2+}
cAMP	=	Cyclic adenosine monophosphate
CL	=	Cardiolipin
CypD	=	Cyclophilin D
Cyt c	=	Cytochrome c
DR4 and DR5	=	Death receptors 4 and 5
FasL	=	Fas ligand
GFAP	=	Glial fibrillary acidic protein
Gpx1	=	Glutathione peroxidase
H_2O	=	Water
H_2O_2	=	Hydrogen peroxide
HCY	=	Homocysteine
HSP70	=	Heat shock protein70
Iba1	=	Calcium-binding adaptor molecule-1
IGF-1	=	Insulin/insulin-like growth factor-1
IL6	=	Interleukin6
MEFs	=	Mouse embryonic fibroblasts
mPTP	=	Membrane permeability transition pore
O_2	=	Oxygen
O_2^-	=	Superoxide
OH-	=	Hydroxyl
PAP7	=	Peripheral-type benzodiazepine receptor-associated protein 7
Pb	=	Lead
PET	=	Positron emission tomography
PKA	=	Protein kinase A
Prx	=	Peroxiredoxin
ROS	=	Reactive oxygen species
SAM	=	S-adenosylhomocysteine
SODs	=	Superoxide dismutases

SP1	=	Specificity protein 1
StAR	=	Steroidogenic acute regulatory protein
TNFR1	=	Tumor necrosis factor receptor 1
TRAIL	=	Tumor necrosis factor-related apoptosis-inducing ligand
TSPO	=	Translocator protein
VDACs	=	Voltage-dependent anion channels

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

PATIENT'S CONSENT

Declared none.

REFERENCES

[1] Cooper DM. The balance between life and death: defining a role for apoptosis in aging. J Clin Exp Pathol 2012; S4:001.

[2] Elmore S. Apoptosis: a review of programmed cell death. Toxicol Pathol 2007; 35(4): 495-516.

[3] Hengartner MO. The biochemistry of apoptosis. Nature 2000; 407(6805): 770-6.

[4] Bin Lu H-DC, Hong-Guang Lu. The relationship between apoptosis and aging. Adv Biosci Biotechnol 2012; 3: 705-11.

[5] Joaquin AM, Gollapudi S. Functional decline in aging and disease: a role for apoptosis. J Am Geriatr Soc 2001; 49(9): 1234-40.

[6] Vinay K, Abul KA, Jon CA. Cell injury, cell death, and adaptations. In: Robbins Basic Pathology. 9th ed: Saunders, An imprint of Elsevier 2012; 1-30.

[7] Robb EL, Page MM, Stuart JA. Mitochondria, cellular stress resistance, somatic cell depletion and lifespan. Curr Aging Sci 2009; 2(1): 12-27.

[8] Fulda S, Gorman AM, Hori O, Samali A. Cellular stress responses: cell survival and cell death. Int J Cell Biol 2010; 2010: 214074.

[9] Lahiri DK, Maloney B, Basha MR, Ge YW, Zawia NH. How and when environmental agents and dietary factors affect the course of Alzheimer's disease: the "LEARn" model (latent early-life associated regulation) may explain the triggering of AD. Curr Alzheimer Res 2007; 4(2): 219-28.

[10] Ott M, Gogvadze V, Orrenius S, Zhivotovsky B. Mitochondria, oxidative stress and cell death. Apoptosis 2007; 12(5): 913-22.

[11] Dai DF, Chiao YA, Marcinek DJ, Szeto HH, Rabinovitch PS. Mitochondrial oxidative stress in aging and healthspan. Longev Healthspan 2014; 3: 6.

[12] Dirks-Naylor AJ, Lennon-Edwards S. Cellular and molecular mechanisms of apoptosis in age-related muscle atrophy. Curr Aging Sci 2011; 4(3): 269-78.

[13] Lahiri DK, Maloney B, Zawia NH. The LEARn model: an epigenetic explanation for idiopathic neurobiological diseases. Mol Psychiatry 2009; 14(11): 992-1003.

[14] Butterfield DA, Reed T, Newman SF, Sultana R. Roles of amyloid beta-peptide-associated oxidative stress and brain protein modifications in the pathogenesis of Alzheimer's disease and mild cognitive impairment. Free Radic Biol Med 2007; 43(5): 658-77.

[15] Lahiri DK, Maloney B. The "LEARn" (Latent Early-life Associated Regulation) model integrates environmental risk factors and the developmental basis of Alzheimer's disease, and proposes remedial steps. Exp Gerontol 2010; 45(4): 291-6.

[16] Lahiri DK. Prions: a piece of the puzzle? Science 2012; 337(6099): 1172.

[17] Shiber A, Ravid T. Chaperoning proteins for destruction: diverse roles of Hsp70 chaperones and their co-chaperones in targeting misfolded proteins to the proteasome. Biomolecules 2014; 4(3): 704-24.

[18] Granholm AC, Boger H, Emborg ME. Mood, memory and movement: an age-related neurodegenerative complex? Curr Aging Sci 2008; 1(2): 133-9.

[19] Woods JA, Wilund KR, Martin SA, Kistler BM. Exercise, inflammation and aging. Aging Dis 2012; 3(1): 130-40.

[20] Rubio-Perez JM, Morillas-Ruiz JM. A review: inflammatory process in Alzheimer's disease, role of cytokines. ScientificWorldJournal 2012; 2012: 756357.

[21] Ricci MS, El-Deiry W. The extrinsic pathway of apoptosis. In: Gewirtz D, Holt S, Grant S, Eds. Apoptosis, senescence, and cancer. New Jersey: Humana Press 2007; pp. 31-54.

[22] Shen J, Tower J. Programmed cell death and apoptosis in aging and life span regulation. Discov Med 2009; 8(43): 223-6.

[23] Paradies G, Petrosillo G, Paradies V, Ruggiero FM. Oxidative stress, mitochondrial bioenergetics, and cardiolipin in aging. Free Radic Biol Med 2010; 48(10): 1286-95.

[24] Paradies G, Paradies V, Ruggiero FM, Petrosillo G. Changes in the mitochondrial permeability transition pore in aging and age-associated diseases. Mech Ageing Dev 2013; 134(1-2): 1-9.

[25] Mattson MP. Apoptosis in neurodegenerative disorders. Nat Rev Mol Cell Biol 2000; 1(2): 120-9.

[26] Roos WP, Kaina B. DNA damage-induced cell death by apoptosis. Trends Mol Med 2006; 12(9): 440-50.

[27] Circu ML, Aw TY. Reactive oxygen species, cellular redox systems, and apoptosis. Free Radic Biol Med 2010; 48(6): 749-62.

[28] Marchi S, Giorgi C, Suski JM, *et al*. Mitochondria-ros crosstalk in the control of cell death and aging. J Signal Transduct 2012; 2012: 329635.

[29] Petrosillo G, Ruggiero FM, Paradies G. Role of reactive oxygen species and cardiolipin in the release of cytochrome c from mitochondria. FASEB J 2003; 17(15): 2202-8.

[30] Gatliff J, Campanella M. The 18 kDa translocator protein (TSPO): a new perspective in mitochondrial biology. Curr Mol Med 2012; 12(4): 356-68.

[31] Papadopoulos V, Lecanu L. Translocator protein (18 kDa) TSPO: an emerging therapeutic target in neurotrauma. Exp Neurol 2009; 219(1): 53-7.

[32] Boatright KM, Salvesen GS. Mechanisms of caspase activation. Curr Opin Cell Biol 2003; 15(6): 725-31.

[33] Widmann C, Gibson S, Johnson GL. Caspase-dependent cleavage of signaling proteins during apoptosis. A turn-off mechanism for anti-apoptotic signals. J Biol Chem 1998; 273(12): 7141-7.

[34] Thornberry NA. Caspases: key mediators of apoptosis. Chem Biol 1998; 5(5): R97-103.

[35] Fischer U, Janicke RU, Schulze-Osthoff K. Many cuts to ruin: a comprehensive update of caspase substrates. Cell Death Differ 2003; 10(1): 76-100.

[36] Nicholson DW, Thornberry NA. Caspases: killer proteases. Trends Biochem Sci 1997; 22(8): 299-306.

[37] Hochreiter-Hufford A, Ravichandran KS. Clearing the dead: apoptotic cell sensing, recognition, engulfment, and digestion. Cold Spring Harb Perspect Biol 2013; 5(1): a008748.

[38] Rupprecht R, Papadopoulos V, Rammes G, *et al*. Translocator protein (18 kDa) (TSPO) as a therapeutic target for neurological and psychiatric disorders. Nat Rev Drug Discov 2010; 9(12): 971-88.

[39] Ukessays.com. United kingdom: [Nov. 2013] . Available from www.ukessays.com/essays/biology/translocator-protein-formerly-known-as-peripheral-benzodiazepine-receptor-biology-essay.php.

[40] Batarseh A, Papadopoulos V. Regulation of translocator protein 18 kDa (TSPO) expression in health and disease states. Mol Cell Endocrinol 2010; 327(1-2): 1-12.

[41] Rampon C, Bouzaffour M, Ostuni MA, *et al*. Translocator protein (18 kDa) is involved in primitive erythropoiesis in zebrafish. FASEB J 2009; 23(12): 4181-92.

[42] Du H, Yan SS. Mitochondrial permeability transition pore in Alzheimer's disease: cyclophilin D and amyloid beta. Biochim Biophys Acta 2010; 1802(1): 198-204.

[43] Veenman L, Shandalov Y, Gavish M. VDAC activation by the 18 kDa translocator protein (TSPO), implications for apoptosis. J Bioenerg Biomembr 2008; 40(3): 199-205.

[44] Barron AM, Garcia-Segura LM, Caruso D, *et al*. Ligand for translocator protein reverses pathology in a mouse model of Alzheimer's disease. J Neurosci 2013; 33(20): 8891-7.

[45] Borowicz KK, Piskorska B, Banach M, Czuczwar SJ. Neuroprotective actions of neurosteroids. Front Endocrinol (Lausanne) 2011; 2: 50.

[46] Kato-Negishi M, Kawahara M. Neurosteroids block the increase in intracellular calcium level induced by Alzheimer's beta-amyloid protein in long-term cultured rat hippocampal neurons. Neuropsychiatr Dis Treat 2008; 4(1): 209-18.

[47] Strous R. Neurosteroids in the Aging Brain. In: Ritsner M, Weizman A, Eds. Neuroactive Steroids in Brain Function, Behavior and Neuropsychiatric Disorders. Netherlands:Springer 2008; pp. 241-8.

[48] Martin LJ. The mitochondrial permeability transition pore: a molecular target for amyotrophic lateral sclerosis therapy. Biochim Biophys Acta 2010; 1802(1): 186-97.

[49] Michael L, Allan DM, Eds. Marks' basic medical biochemistry: a clinical approach 3rd edition. Philadelphia: Lippincott Williams & Wilkins 2009; pp. 383-401.

[50] Miller WL. Steroidogenic acute regulatory protein (StAR), a novel mitochondrial cholesterol transporter. Biochim Biophys Acta 2007; 1771(6): 663-76.

[51] Liu J, Li H, Papadopoulos V. PAP7, a PBR/PKA-RIalpha-associated protein: a new element in the relay of the hormonal induction of steroidogenesis. J Steroid Biochem Mol Biol 2003; 85(2-5): 275-83.

[52] Liu J, Rone M, Papadopoulos V. PAP7 is a steroidogenesis signal transporter from golgi apparatus to mitochondria in mouse MA-10 leydig cells. FASEB J 2007; 21:328.1.

[53] Rone MB, Fan J, Papadopoulos V. Cholesterol transport in steroid biosynthesis: role of protein-protein interactions and implications in disease states. Biochim Biophys Acta 2009; 1791(7): 646-58.

[54] Kumar A, Muzik O, Shandal V, Chugani D, Chakraborty P, Chugani HT. Evaluation of age-related changes in translocator protein (TSPO) in human brain using (11)C-[R]-PK11195 PET. J Neuroinflammation. 2012; 9: 232.

[55] Gulyas B, Vas A, Toth M, *et al*. Age and disease related changes in the translocator protein (TSPO) system in the human brain: positron emission tomography measurements with [11C]vinpocetine. Neuroimage 2011; 56(3): 1111-21.

[56] Chen MK, Guilarte TR. Translocator protein 18 kDa (TSPO): molecular sensor of brain injury and repair. Pharmacol Ther 2008; 118(1): 1-17.

[57] Lin R, Angelin A, Da Settimo F, *et al*. Genetic analysis of dTSPO, an outer mitochondrial membrane protein, reveals its functions in apoptosis, longevity, and Aβ42-induced neurodegeneration. Aging Cell 2014; 13(3): 507-18.

[58] Rojas S, Martin A, Arranz MJ, *et al*. Imaging brain inflammation with [(11)C]PK11195 by PET and induction of the peripheral-type benzodiazepine receptor after transient focal ischemia in rats. J Cereb Blood Flow Metab 2007; 27(12): 1975-86.

[59] Park SY, Cho N, Chang I, *et al*. Effect of PK11195, a peripheral benzodiazepine receptor agonist, on insulinoma cell death and insulin secretion. Apoptosis 2005; 10(3): 537-44.

[60] Veenman L, Papadopoulos V, Gavish M. Channel-like functions of the 18-kDa translocator protein (TSPO): regulation of apoptosis and steroidogenesis as part of the host-defense response. Curr Pharm Des 2007; 13(23): 2385-405.

[61] Rodrigo Medeiros MAC, Frank ML. Elucidating the triggers, progression, and effects of Alzheimer's Disease. J Alzheimers Dis 2013; 33(Suppl 1): S195-210.

[62] Karlstetter M, Nothdurfter C, Aslanidis A, *et al*. Translocator protein (18 kDa) (TSPO) is expressed in reactive retinal microglia and modulates microglial inflammation and phagocytosis. J Neuroinflammation 2014; 11: 3.

[63] Ryu JK, Choi HB, McLarnon JG. Peripheral benzodiazepine receptor ligand PK11195 reduces microglial activation and neuronal death in quinolinic acid-injected rat striatum. Neurobiol Dis 2005; 20(2): 550-61.

[64] Ji B, Maeda J, Sawada M, *et al*. Imaging of peripheral benzodiazepine receptor expression as biomarkers of detrimental versus beneficial glial responses in mouse models of Alzheimer's and other CNS pathologies. J Neurosci 2008; 28(47): 12255-67.

[65] Taliani S, Pugliesi I, Da Settimo F. Structural requirements to obtain highly potent and selective 18 kDa translocator protein (TSPO) ligands. Curr Top Med Chem 2011; 11(7): 860-86.

[66] Ching AS, Kuhnast B, Damont A, Roeda D, Tavitian B, Dolle F. Current paradigm of the 18-kDa translocator protein (TSPO) as a molecular target for PET imaging in neuroinflammation and neurodegenerative diseases. Insights Imaging 2012; 3(1): 111-9.

Received: August 17, 2014 Revised: October 31, 2014 Accepted: December 09, 2014