Triphenylphosphonium (TPP) Cation as a Promising Strategy in Mitochondria-Targeting and the Current Studies of the TPP-Based Mitochondria-Targeting Medicines in Ischemia-Reperfusion Injury and Cancer

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Abstract: Mitochondria are known as the "powerhouse" of a cell, in charge of the generation of respiratory ATP. On the other hand, mitochondria are also involved in cell metabolism, the formation and regulation of reactive oxygen species (ROS), mitophagy, and cell signalling. As a result, diseases like ischemia-reperfusion (IR) injury, neurological disorders, diabetes, and cancer may be caused by mitochondrial malfunction. Hence, mitochondrial dysfunction treatment has become a great interest in the research direction for the therapeutic strategy. To treat the dysfunctional mitochondria and facilitate the transportation of drugs, we need to accomplish accurate mitochondria-targeting. In this review, I will discuss triphenylphosphonium (TPP) as one of the most prevalent strategies in targeting and facilitating the drugs into mitochondria. Furthermore, the current studies of TPP in IR injury and cancer resulting from mitochondria dysfunction will be reviewed.
Keywords: Triphenylphosphonium; Mitochondria-Targeting; Cancer; Ischemia-Reperfusion Injury

Introduction

Mitochondria are important organelles responsible for multiple functions. The dysfunction of mitochondria could result in IR injury, cancer, diabetes and some neurological disorders. [1] Mitochondrial dysfunction is related to many high-prevalence diseases, thus it will provide a huge potential contribution to saving countless lives and medical resources. The concept of mitochondria-targeting is important because conventional drug delivery systems to mitochondria have shown unfavourable outcomes such as low bioavailability, poor biodistribution, lack of water solubility, side effects, drug resistance, low therapeutic response despite high dosages, and unable to penetrate through the barriers in the body[2].

It is very challenging in developing a mitochondria-targeting drug, as mitochondria possess different barriers to molecule transmission which are different from other organelles. The mitochondrion is enclosed by a double-layer membrane, and the inner membrane is folded into cristae according to the baffle model. The current strategies for mitochondria drug delivery could be divided into active and passive targeting. Limited by its morphological properties, passive targeting is difficult to achieve, hence active delivery is the mainstream of the current study. Active targeting is referred to the specific interactions that happen at mitochondrial sites, including antigen-antibody binding and ligand-receptor associations. The rationale behind active targeting is to take advantage of the compatibility between the mitochondrial compartment and the carrier molecule's physicochemical features (electric charge, hydrophilicity, size, and mass). To date, the common methods and pharmacological approaches toward mitochondria-targeting are lipophilic cations, nanotechnology, cationic plastoquinone derivatives, mitochondrial uncoupling, and peptide-based targeting[2]. Among these methods, the TPP which belongs to the lipophilic cations category has proven to be a strong candidate. Herein this review

will provide an overview of the advancement of TPP and TPP-based mitochondria-targeted medicines in IR injury and cancer.

1. Overview of Triphenylphosphonium (TPP)

TPP is the most researched lipophilic cation among mitochondrial targeting strategies at the moment. It is a member of the group of tertiary phosphines, which are phosphanes with three hydrogens substituted by phenyl groups (Fig.1) [3]. The localization and uptake of TPP by the mitochondria are based on 1) TPP's hydrophobic surface; 2) TPP possesses low activation energy for the transportation across the hydrophobic membrane core; 3) The huge potential difference between mitochondria inner membrane and TPP molecules.

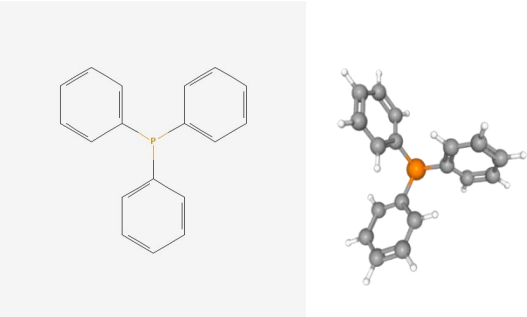

Figure 1. 2D and 3D structure of TPP. [3]

First, TPP could easily pass through the mitochondria's phospholipid because of its high hydrophobicity. This property is proportional to the ability to cross through the cell membrane. TPP's hydrophobic surface causes the high affinity between the mitochondria's phospholipid bilayer and the TPP compound itself, thus creating a pathway through the membrane.

Second, TPP has a unique property which is the low activation energy for transportation across the hydrophobic membrane core. This property is the main feature that differentiates TPP from other common lipophilic cations. Due to the three hydrophobic phenyl groups, the TPP cation possesses a big ionic radius. The activation energy required to drive the cation into the membrane is inversely related to the ionic radius. Hence, this makes TPP has lower activation energy in penetrating biological membranes.

Last, the potential difference drives the transportation of TPP-based compounds into mitochondria. The TPP-compounds are bringing positive charges, while the mitochondrial membrane potential is negatively-charged (150-180mV). The strong negative membrane potential of mitochondria is found nowhere else in the cell, resulting in exceptional molecular selectivity. The huge potential difference between them is the primary force that drives TPP into mitochondria. Furthermore, the Nernst equation states that for every 60mV of membrane potential, the absorption of these TPP-compounds is around 10-fold higher, resulting in a substantial uptake into mitochondria. [4][5]

2. TPP-based Mitochondria-targeted Compounds with the Common Diseases

As mentioned before, mitochondria have several important functions in the human body and dysfunctional mitochondria will lead to many diseases. This paper will elaborate on the current studies of TPP-based mitochondria-targeted compounds on IR injury and cancer.

2.1 Ischemia-Reperfusion (IR) Injury

Ischemia-reperfusion (IR) injury happens when a tissue's blood flow is interrupted (ischemia) and then restored

(reperfusion). IR injury is a very commonly happening situation in clinical settings such as myocardial infarction, stroke, hypovolemic shock, or organ transplantation. Furthermore, It's also related to many significant clinical symptoms, including multiple organ dysfunction syndromes, brain dysfunction, and sudden heart failure. The currently mainstream belief suggests for the cause of IR injury is mainly because of the sudden increase of reactive oxygen species (ROS) production at the reperfusion stage. Mitochondria produce most of the ATP by OXPHOS and are also the primary source of ROS. ROS produced by mitochondria is an important signalling molecule and actor in many cellular adaptive mechanisms. The ROS become toxic when the redox equilibrium is disrupted and will result in IR injury [6].

Current research on TPP-based mitochondria-targeted drugs for IR injury is the mitochondria-selective S-nitrosating agent (MitoSNO). MitoSNO is a mitochondria-targeted drug that prevents complex I from producing reactive oxygen species (ROS) during early reperfusion following IR injury. MitoSNO is made up of the NO donor S-nitroso-N-acetylpenicillamine and the TPP cation. MitoSNO will be driven into the mitochondrial matrix within a few minutes after intravenous injection. MitoSNO immediately binds with intramitochondrial thiols and S-nitrosated cysteine 39 on complex I subunit ND3, leaving the enzyme inactive and preventing an uncontrolled burst of ROS upon reperfusion. MitoSNO not only protected against IR injury in vivo but also showed a drastically improved long-term cardiac performance after IR injury[7].

2.2 Cancer

There are many mechanisms explaining the relationship between cancer and mitochondria dysfunction. The 5 mainstreams beliefs are 1) The DNA mutations that affect mitochondria, causing the alterations of the electron transport chain's subunits; 2) The abnormal oxidative stress from the ROS as the stimulus for cancer generation; 3) The dysregulation of mitochondria's apoptosis function; 4) The metabolic reprogramming concerning several mutations in genes encoding TCA cycle enzymes; 5) Multiple molecular changes result in long-term cellular proliferation.[1][8]

TPP-based Mitocans primarily target cancer cells with high mitochondrial membrane potential and deliver medications or bioactive substances to the cancer cell mitochondria to achieve therapeutic or cytotoxic goals. The majority of these compounds target a specific element of cancer cell mitochondrial operations, such as high levels of reactive oxygen species (ROS), aberrant oxidative phosphorylation, or other physiological functions (11). To date, there are many ongoing pieces of research on the development of Mitocans. All the designs are categorized according to their rationale in dealing with cancer. The types of anticancer agents are, 1) TPP-linked antioxidants: MitoQ, Mito-CP and Mito-ChM; 2) TPP-linked with natural products: Mito-resveratrol, Mito-HNK and Mito-dihydro; 3) TPP-linked with commercialized drugs: Mito-chlorambucil, Mito-metformin, and Mito-doxorubicin; 4) TPP-linked with enzyme inhibitors: DPC, DAP and DCA; 5) TPP-linked with photosensitizers: MitoPhotoDNP and Mito-CCy; 6) TPP-linked with thermo-sensitive agents: TPPV; 7) TPP-linked with small cytotoxic molecules: APPI, APPCL and MitoDNP-SUM.[2][4][5]

Numerous investigations were conducted for decades on the possibility of non-targeted treatment to restore the normal physiology of mitochondria. In general, the outcomes are less than ideal, therefore researchers are currently focused on developing a mitochondrial-targeting strategy. Mitochondria stand up as a prominent therapeutic target when considering their involvement in human pathophysiology. Multiple drugs with distinct targets and modes of action have been produced to treat mitochondrial dysfunction in various clinical circumstances. This paper has covered the properties and applications of TPP as the mitochondria-targeted strategy.

Furthermore, several innovative delivery mechanisms such as cationic plastoquinone derivatives, peptide-based targeting, nanotechnology and mild mitochondrial uncoupling are also showing great potential and are now being evaluated.Many of these treatments appear promising based on in vitro or cell-free outcomes; however, more research, especially in vivo, is needed to guarantee that findings are translated to clinically relevant settings. To evaluate a compound's

ability to prevent and/or treat mitochondrial dysfunction, specific animal illness models are required. Finally, human clinical studies in physiologically appropriate situations are required to determine the therapeutic utility of these compounds.

Conclusion

In summary, this paper has provided a general introduction to TPP and its current progress in the treatment of IR injury and cancer. Mitochondria therapeutic approach is actually in its infancy, many further investigations still need to be done such as the dosage pattern, the long-term effect, side effects, best administration method and time. However, according to the current research direction focusing on mitochondria as the therapeutic target seems to be a glimpse of light on many diseases that have been haunting humankind.

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