



## MITOCHONDRIAL PERMEABILITY TRANSITION PORES: ANOTHER VIEW

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### ABSTRACT

Mitochondria have been considered as the powerhouse of the cell that is mainly responsible for the cell energy by taking part in various biological reactions. Moreover, the mitochondria play an important role in the pathological conditions by increasing permeability transition of the mitochondrial membrane that may enhance the charge potential of the mitochondria. Mitochondrial permeability transition pores (MPTPs) are the pore present on the inner mitochondrial membrane. The components of the MPTP are adenine nucleotide translocase (ANT), cyclophilin-D (CyP-D) and voltage dependent anion channel (VDAC). They have been noted to open in order to maintain various pathological conditions such as cell apoptosis, ischemia/reperfusion (I/R) injury, heart failure and certain other cardiovascular diseases. It also plays an important role in various cytoprotective mechanisms. The present review explains about the structure and physiological functions associated with MPTP.

**Keywords:** Mitochondrial permeability transition pore, Pathological, Cardiovascular.

### INTRODUCTION

Mitochondrial permeability transition involves the formation of proteaceous and regulated pores by the apposition of inner and outer mitochondrial membrane proteins. These proteins have been noted to cooperate to form the mitochondrial megachannel<sup>1-2</sup>. Mitochondrial permeability transition pores (MPTPs) are the pores that are distributed all over the body amongst body cell's mitochondria<sup>3-4</sup>. MPTP only allow the passing of the molecules having a molecular weight of less than 1500 Daltons. Moreover, the components of the MPTP pores have been well identified that include include ANT, CyP-D and VDAC<sup>5-7</sup>. It has been suggested that MPTP opening via ANT is a result of difference in the cytoplasmic side (c-state) and inner matrix side (m-state) of mitochondria. Furthermore the CyP-D associated MPTP opening results by inhibiting the binding site of the cyclosporine A (CsA), whereas, the VDAC opens the MPT pore by opening of Ca<sup>2+</sup> channels<sup>8-9</sup>. Various pathological states have been well reported that lead to the opening of MPTP which include apoptosis, I/R and heart failure. In addition, other conditions including necrosis, cardiomyopathy and many cardiovascular diseases have also been reported<sup>10-14</sup>. The present review explains about the structure of MPT pores. Moreover, role of MPTP in various pathological states have been critically discussed in this review.

### STRUCTURE OF MPTP

MPTP are the pores made up of protein that are present on the inner membrane of the mitochondria and only allow the molecules having molecular weight of 1500 Daltons to pass through. However, studies about the complete structure of MPTP have been lacking but little information has been reported about the structure of MPTP<sup>15</sup>. Three components in the MPTP structure has been identified comprehensively that include ANT, CyP-D and VDAC<sup>5-7</sup>. In contrast, it has been suggested that MPTP is more disposed to the ANT ligands. In a large number of nucleotides, permeability transition (PT) pore interact with substrates of ANT, i.e., ADP, dADP and ATP<sup>7</sup>. Moreover, the binding of the ANT ligands through c-state PT pore was activated while the m-state PT pore was inhibited. Thus, it may be suggested that c-state is essential for the opening of MPTP<sup>6</sup>. Further, when the pure form of the

ANT is integrated into liposomes, a selective change occurs in the state of ANT from a selective antiporter to a non-selective pore<sup>16</sup>. Moreover, it was reported that the ANT in cytoplasmic-state collapse into a non-selective pore with more Ca<sup>2+</sup> ion concentration. Further, it has been studied that the rate of closing the MPTP depends on the occurrence of pore opening<sup>5</sup>. The conformational change has been known to occur in between c-state and m-state due to ANT, the binding energy of which is provided by the intermediate state of carrier. The second component of the MPTP is CyP-D, which is a hydrophilic protein that is capable to bind strongly with inner mitochondrial membrane component<sup>17</sup>. It has been known that cyclosporine-A (CSA) blocks the MPTP. Moreover, it has also been found that CyP-D bound in the same manner and in same amount as that of CSA. The activity of CyP-D get enhanced by the presence of ADP and reduced in presence of Ca<sup>2+</sup> ions. The third component of the MPTP is VDAC, which is mainly present on the outer membrane of mitochondria and plays an important role in the movement of various substances and in the permeability transition. It has been vitally studied that anti-VDAC antibodies prevent the opening of MPTP induced by Ca<sup>2+</sup> ions<sup>18</sup>.

### PATHOLOGICAL ROLE OF MPTP

Ample of studies have reported that MPTP play vital roles in order to maintain various pathological conditions such as cell apoptosis, I/R injury, heart failure and various cytoprotective mechanisms<sup>10-14</sup> (Fig 1). However, it is still not clearly understood that CsA sensitive MPTP is involved in the cell apoptosis<sup>19</sup>. Although, researchers studied on CyP-D deficient mice and concluded that MPTP is not necessary for cell apoptosis, while in some of the cases it has been seen that apoptosis is mediated by CsA sensitive MPTP and is ultimately inhibited by CsA. In addition, it has been demonstrated that CsA in high concentration inhibits cytoplasmic CyP-D and thus cause apoptosis<sup>20</sup>. Various studies on CyP-D showed that activation prevents cell apoptosis ultimately inhibiting it<sup>20-21</sup>. It is emphasized that this inhibition is associated with CsA sensitive MPTP. Moreover, the insufficient overexpression of CyP-D in

apoptosis activates necrotic cell death via CyP-D dependent MPTP<sup>22-23</sup>.

Moreover, numerous studies have reported that some factors in ischemia induce MPTP opening, ATP depletion, Ca<sup>2+</sup> overload and phosphate buildup. In contrast, in DOG (2-deoxy-glucose) method, it has been shown that MPTP opening occurs in reperfusion not in ischemia. During ischemia, low pH occurs inside the heart which competitively binds Ca<sup>2+</sup> to the receptor site of ANT resulting in ROS production, which further leads to increased Ca<sup>2+</sup> overload ultimately causing MPTP opening<sup>24</sup>. It has been suggested that during reperfusion some of the MPTPs remains closed for the recovery of mitochondria. The cells showed their normal physiological functions after ischemia, when ATP synthesis, decrease Ca<sup>2+</sup> overload and decreased ROS production restored in undamaged mitochondria<sup>25-26</sup>.

Further, Heart failure (HF) has been considered as a severe disease caused by decrease energy metabolism, Ca<sup>2+</sup> imbalance and ROS generation that may accelerate MPTP opening<sup>27</sup>. Moreover, the MPTP opening in myocardial infarction and Ca<sup>2+</sup> induced cardiomyopathy has also been reported to be the leading cause of HF<sup>28</sup>. The role of MPTP in HF has been further confirmed by the results obtained from the studies performed by DOG method in both I/R and HF<sup>27-29</sup>.

In addition, MPTP has vital roles to play in the pathogenesis of cytoprotective mechanisms. It has been studied that ROS and Ca<sup>2+</sup> are the main precursor for the opening of MPTP during cancer<sup>30-31</sup>. It has been seen that cancer cells activate the antioxidant system and enhances the activity of superoxide dismutase enzyme which decrease activity of oxidative stress and thus results in MPTP opening<sup>32</sup>. Moreover, the cancer cells possess the ability to carry the transportation of Ca<sup>2+</sup> present in the cytosol [33]. Studies have also explained about the expression of the MPTP components in cancer. The VDAC has been noted to enhance the MPTP opening; ANT reduce the upregulation of MPTP while CyP-D posses inhibitory effects of MPT pore<sup>34-35</sup>. Furthermore, role of MPTP in cancer has been confirmed by the fact that in cancer treatment, patients are subjected to mitochondrial chemotherapy to induce cell apoptosis in the tumor cells ultimately preventing cell differentiation of the tumor cells<sup>36</sup>. Thrombosis can be defined as the deposition of the lipoprotein in the coronary artery which may lead to various diseases like coronary thrombosis, anoxia and ischemia<sup>37</sup>. It has been shown that CsA induced the releasing of cytochrome C by inhibiting proapoptotic signals. It has also been found that CsA is the competitive inhibitor of CyP-D which is the important component of the MPTP<sup>37-38</sup>. Thus it can be concluded that MPTP is the primary target of CsA.

## CONCLUSION

MPTP have been found to be effective in the therapeutic targeting of various cardiovascular as well as other life threatening diseases such as I/R, HF, cancer and cell apoptosis. Various types of chemicals have been vitally studied in order to improve the pharmacological profile of MPTPs. Although, the present review explained about the role of MPTP in various cardiovascular and non-cardiovascular diseases, but further studies are in demand in order to completely understand the structure and regulation of MPTP so that novel therapeutic drugs can be designed to improve the quality of life in various pathological states.

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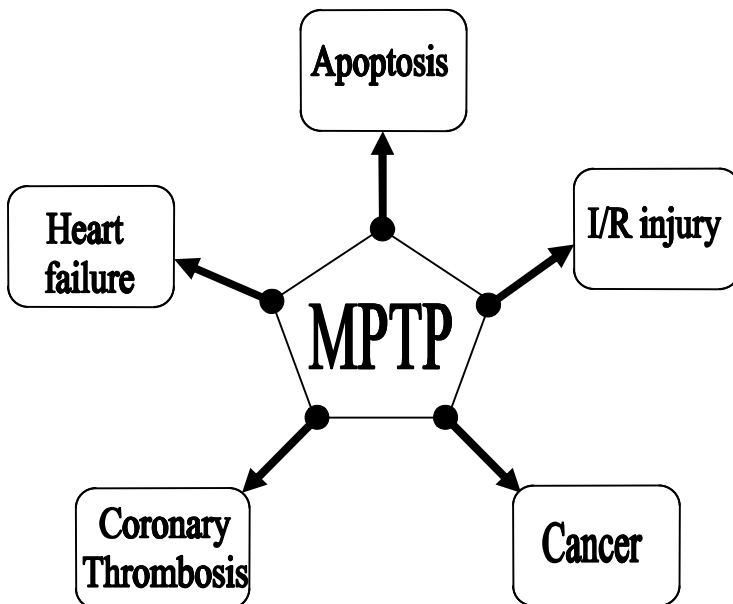


Figure 1. Roles of MPTP in various pathological diseases