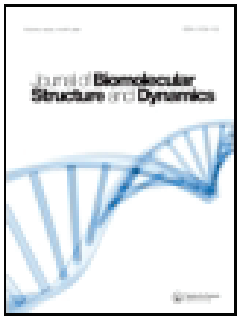

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Anastrozole-mediated modulation of mitochondrial activity by inhibition of mitochondrial permeability transition pore opening: an initial perspective

Somesh Kumar[a], Neha Choudhary[b], Mohammed Faruq[c], Arun Kumar[d,e], Ravindra K. Saran[f], Prem Kumar Indercanti[g], Vikram Singh[b], Haseena Sait[a], Sunita Jaitley[h], Martin Valis[i], Kamil Kuca[j], Sunil K. Polipalli[a], Manoj Kumar[d,k], Tejveer Singh[l]*, Prashanth Suravajhala[m], Rohit Sharma[n] and Seema Kapoor[a]

[a]Pediatrics Genetics & Research Laboratory, Department of Pediatrics, Maulana Azad Medical College & Associated LN Hospital, Delhi, India; ; [b]Centre for Computational Biology and Bioinformatics, Central University of Himachal Pradesh, Dharamsala, India; [c]Institute of Genomics and Integrative Biology, Council of Scientific and Industrial Research (CSIR), Delhi, India; [d]Department of Emergency Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India; [e]Department of Zoology, Kirori Mal College, University of Delhi, Delhi, India; [f]Department of Pathology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, Delhi, India; [g]Institute of Nuclear Medicine & Allied Sciences, (DRDO), Delhi, India; [h]Department of Biomedical Sciences, Acharya Narendra Dev College, University of Delhi, Delhi, India; [i]Department of Neurology of the Medical Faculty of Charles University and University Hospital in Hradec Králové, Hradec Králové, Czech Republic; [j]Department of Chemistry, Faculty of Science, University of Hradec Králové, Hradec Králové, Czech Republic; [k]Department of Microbiology, World College of Medical Science and Research, Jhajjar, Haryana, India; [l]Molecular Oncology Laboratory, Department of Zoology, University of Delhi, Delhi, India; [m]Amrita School of Biotechnology, Amrita University, Clappana PO, Kerala, India; [n]Department of Rasa Shastra and Bhaishajya Kalpana, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

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ABSTRACT

The mitochondrial permeability transition pore (mtPTP) plays a vital role in altering the structure and function of mitochondria. Cyclophilin D (CypD) is a mitochondrial protein that regulates mtPTP function and a known drug target for therapeutic studies involving mitochondria. While the effect of aromatase inhibition on the mtPTP has been studied previously, the effect of anastrozole on the mtPTP has not been completely elucidated. The role of anastrozole in modulating the mtPTP was evaluated by docking, molecular dynamics and network-guided studies using human CypD data. The peripheral blood mononuclear cells (PBMCs) of patients with mitochondrial disorders and healthy controls were treated with anastrozole and evaluated for mitochondrial permeability transition pore (mtPTP) function and apoptosis using a flow cytometer. Spectrophotometry was employed for estimating total ATP levels. The anastrozole–CypD complex is more stable than cyclosporin A (CsA)–CypD. Anastrozole performed better than cyclosporine in inhibiting mtPTP. Additional effects included inducing mitochondrial membrane depolarization and a reduction in mitochondrial swelling and superoxide generation, intrinsic caspase-3 activity and cellular apoptosis, along with an increase in ATP levels. Anastrozole may serve as a potential therapeutic agent for mitochondrial disorders and ameliorate the clinical phenotype by regulating the activity of mtPTP. However, further studies are required to substantiate our preliminary findings.

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Anastrozole; mitochondrial permeability transition pore; mitochondrial disorders; molecular docking; MD simulation; protein targets; binding sites; docking complexes; structural modelling

1. Introduction

Mitochondrial disorders are a group of inherited disorders that arise when mitochondria fail to harvest sufficient energy for the body to function properly. Due to their diverse genetic and clinical manifestations, the resultant complex phenotypes often pose a diagnostic challenge. Due to the multiple steps involved in energy synthesis, the amelioration of symptoms in these disorders with a single point of is often a difficult action. To date, no single compound is known to ameliorate the phenotype by acting on the multiple steps that lead to mitochondrial dysfunction. Therefore, it is important to develop an alternative drug that can be considered a next-generation modulator of mitochondria. Mitochondrial dysfunction usually (primarily due to mutations specific to mitochondrial genes) results in increased matrix calcium. Calcium (Ca^{2+}) overload across the mitochondrial membrane results in the excessive production of oxygen-derived free radicals. This triggers the opening of the mega transition pore (Halestrap , 2009), also known as the mitochondrial permeability transition pore (mtPTP), an phenomenon first proposed by Hunter and Haworth (1979), which is later functionally characterized separately by various other studies (Kinnally et al., 1989; Petronilli

CONTACT Seema Kapoor drseemakapoor@gmail.com; Somesh Kumar someshsloane@gmail.com Pediatrics Genetics & Research Laboratory, Department of Pediatrics, Maulana Azad Medical College & Associated LN Hospital, Delhi, India.
*Department of Zoology, Hansraj College, University of Delhi, Delhi, India.

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et al., 1989; Sorgato et al., 1987). It is a complex structure comprising several protein domains such as a voltage-dependent anion channel (VDAC) in the outer membrane, adenine nucleotide translocator (ANT) in the inner membrane, cyclophilin D (CypD) in the matrix, and several other molecules (Tsujimoto & Shimizu, 2007). However, it is important to note that newer findings are showing that the core structure of the mtPTP is not fully understood. Under normal conditions, the mitochondrial matrix contains CypD and the mtPTP remains closed. Its opening is finely regulated by a plethora of factors, including changes in ionic Ca^{2+}, pH, reactive oxygen species (ROS), adenosine diphosphate/adenosine triphosphate (ADP/ATP) levels and the expression of B-cell lymphoma-2 (Bcl-2), an anti-apoptotic protein (Rao et al., 2014). The sustained opening of mtPTP channels results in a loss of mitochondrial membrane potential, the uncoupling of oxidative phosphorylation (OXPHOS), matrix swelling, ATP depletion and increased production of reactive oxygen species, ultimately leading to cell death (Nguyen et al., 2013). The depolarization of the mitochondrial membrane potential ($\Delta\psi m$) changes the dynamics of ATP synthase, leading to reduced ATP production. This accelerates the cascade leading to energy depletion, secondary to cellular apoptosis (Figure 1). Excessive calcium overload, ROS production and ATP depletion may cause severe oxidative stress, consequently the extent of PTP opening becomes catastrophic and necrotic cell death turns to be inevitable. However, if the insult is more moderate, PTP opening might only be transient, as some mitochondria reseal during reperfusion. This would allow mitochondria to restore ATP production by oxidative phosphorylation thus possibly allowing the cell to avoid necrosis. The distribution of $\Delta\psi m$ could thus be considered a potential prognostic factor for assessing the degree of tissue dysfunction or damage (Zoratti & Szabò, 1995). mtPTP is a tetramer structure composed of CyP Cyclophilin-D, ANT, VDAC, TSPO and PiC. However functional studies ruled out the importance of PiC as a core regulator of mtPTP and the studies validated it as an additional regulator (Gutiérrez-Aguilar et al., 2014; Kwong et al., 2014; Varanyuwatana & Halestrap, 2012). Also for the TSPO, known as peripheral benzodiazepine receptor too, was functionally characterized as a non-regulator for mtPTP functioning (Šileikytė et al., 2014). So the study was designed to evaluate the CyP-D, ANT and VDAC and their interaction with anastrozole. Also various genetic studies demonstrated that ANT, VDAC and PiC play a regulatory rather than structural role in mtPTP formation (Gutiérrez-Aguilar et al., 2014; Kwong et al., 2014; Varanyuwatana & Halestrap, 2012). The studies of mtPTP structure supporting the ATP synthase nature of permeability transition pore, suggested the complete knockout of the main membrane-embedded component of the ATP synthase, The c-subunit, resulted in no change in the sensitivity of mtPTP to calcium (He, Carroll, et al., 2017; He, Ford, et al., 2017). Previous studies comprising, CyP-D has been evaluated as a potential drug target not only for one set of diseases but also for multiple sets of disorders or

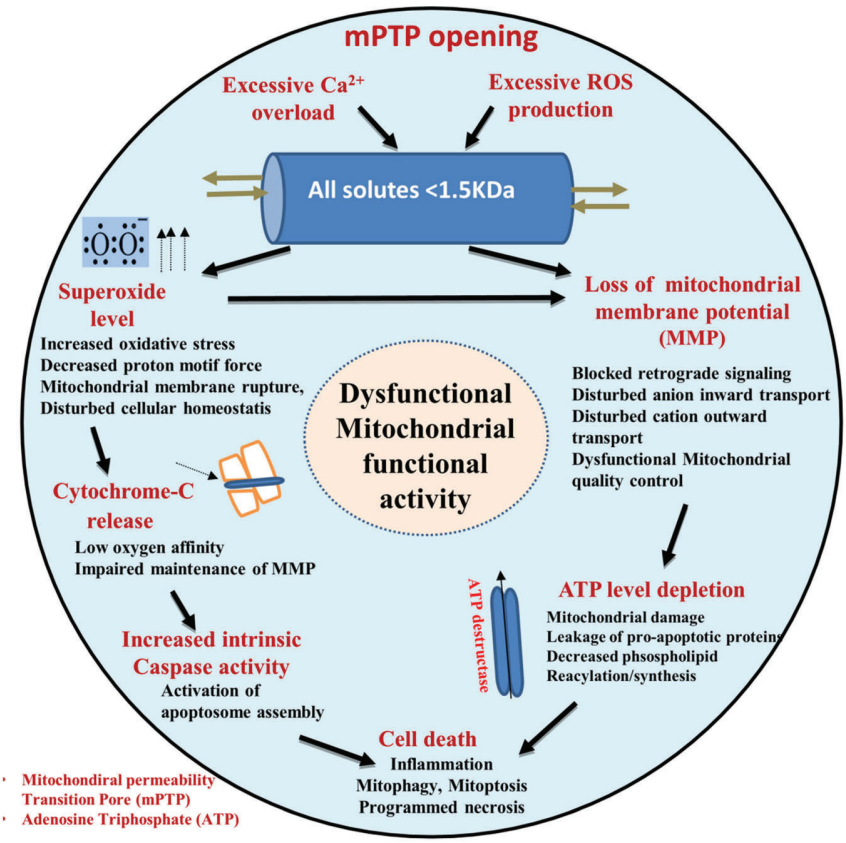

Figure 1. The cascades of mitochondrial dysfunctional events related to the opening of mtPTP: The mtPTP opening allows the release of molecules up to 1500 daltons in size, leading to cascades of unfavorable events such as 514 mitochondrial swelling, the rupture of the outer mitochondrial membrane, leading to the release of cytochrome 515 c into the cytosol, the loss of mitochondrial membrane potential, and the depletion of ATP.