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Membrane Permeability Transition and Dysfunction of Rice Mitochondria Effected by Er(III)

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Abstract Herein, the biological effects of heavy rare earth ion Er(III) on rice mitochondria were comprehensively investigated mainly by spectroscopic methods. The experimental results demonstrated that Er(III) could lead to the swelling of rice mitochondria, collapse of mitochondrial transmembrane potential, decrease of membrane fluidity, promotion of H^+ permeability and suppression of K^+ permeability. These further indicated that Er(III) could induce the mitochondrial permeability transition (MPT) and the dysfunction of rice mitochondria. The ultra-structure change of mitochondria observed by transmission electron microscopy (TEM) also proved that Er(III) induced MPT. Moreover, the testing results of the protective effect of four different agents on mitochondrial swelling implied that the thiol chelation on the mitochondrial inner membrane was the main reason that caused the MPT.

Keywords Erbium · Rice mitochondria · Mitochondrial permeability transition (MPT) · Dysfunction · Spectroscopy

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Introduction

In recent years, rare earth elements (REEs) have received extensive attentions owing to their unique optic and physiological characteristics. REEs are substantially applied in the field of steal, glass, electronic, and petroleum (Atwood 2013). Besides, it was reported that light REEs can promote the germination of seeds, stimulate the growth of roots, enhance the resistance of crops, and improve the yields at a certain degree, and thus, the light REEs have been widely applied in agriculture (Buckingham et al. 1999; Hu et al. 2002; Tyler 2004; Li et al. 2012). Ma (Ma et al. 2010) analyzed the phytotoxicity of rare earth oxide nanoparticles on root elongation of plants and it demonstrated that the Ce^{3+} and La^{3+} ions released from the nanoparticles had negligible effects on the root elongation. Diatloff E, Smith FW, and Asher CJ (Diatloff et al. 1995a, b, c) evaluated the effects of lanthanum and cerium on root elongation of corn and mungbean and further studied the responses of corn and mungbean to low concentrations of lanthanum and cerium in dilute, continuously flowing nutrient solutions. However, these researches are mainly limited to light REEs and their complexes, heavy REEs have not yet caused adequate attention on agriculture and there are very few researches in this field. Moreover, with the increasingly serious environment pollution, heavy REEs are apt to entering environment from discarded metallic devices, and further contaminate soil and water; and what is more serious, with their accumulate in plants and water, they can in turn accumulate in the human bones, kidneys, liver, and so on from the food chain, which may have unfavorable effects on the health of human being (Emsley 2011). In view of the above-mentioned facts, it is necessary to figure out what kinds of physiological impacts heavy REEs have on plants.

Erbium is a trivalent metallic element of the heavy rare earth group and because of its emission at 1,550 nm, erbium is substantially used as photographic filter and metallurgical additive (Parish et al. 1999; Haynes et al. 2012). In order to clarify the physiological effects of erbium on plants, the mitochondria of Hybrid rice Fengyou 9 was chosen in the present work. This is because Hybrid rice Fengyou 9 has been widely cultivated in China owing to its high yield, excellent grain quality, and wide adaptability; and mitochondrion, which is the cell organelle that mainly charged for the energy production and thus been called as the "power house" of the cell by the scientists, also plays a vital role in the respiration and metabolism of plants (Logan 2006).

As reported by Xiong et al. (Xiong et al. 2004), mitochondria can undergo a short time's opening in the inner membrane, namely the mitochondrial membrane permeability transition (MPT), which might lead to many structural and biological functional changes of mitochondria, including the most obvious phenomenon of swelling. Supposing that the MPT has happened, it will further cause the collapsing of transmembrane potential ($\Delta\Psi_m$), releasing of ions and solutes and the eventually ruptured of the outer mitochondrial membrane (Halestrap et al. 2004; Di Lisa and Bernardi 2006; Crompton 1999). In view of the above reasons, spectroscopic methods have been adopted in the present work to investigate the effects of Er(III) on the mitochondrial swelling, transmembrane potential ($\Delta\Psi$m), membrane fluidity, and membrane permeability to H^+ and K^+ of mitochondria isolated from Hybrid rice Fengyou 9. Transmission electron microscope (TEM) has been applied to observe the morphology and ultra-structure changes of the rice mitochondria after the affection of Er(III). The effects of four different protective agents on mitochondrial swelling have also been studied to find out the probable pathway that Er(III) induced MPT.

Materials and Methods

Chemicals

Adenosine diphosphate (ADP), bovine serum albumin (BSA), cyclosporin A (CsA), dithiothreitol (DTT), ethylene glycol bis(2-aminoethyl) tetraacetic acid (EGTA), hematoporphyrin (HP), monobromobimane$^+$ (MBM$^+$), oligomycin, rhodamine 123 (Rh123), rotenone, and valinomycin were all purchased from Sigma (St. Louis, MO). All other reagents were of analytical grade, and all solutions were prepared using asepsis double-distilled water.

Plant Material

Hybrid rice Fengyou 9 (obtained from Longping High-Tech Agriculture CO., Ltd., P. R. China) seedlings were grown in water at dark for about 9 days at the temperature of 35 °C with the water changed twice a day. When the etiolated seedlings grew to 9–10 cm long, their stems (approximately 100 g fresh weight) were cut into pieces for the isolation of mitochondria.

Mitochondrial Isolation

The isolation of rice mitochondria refers to standard differential centrifugation procedures as previous described (Xia et al. 2013). The rice tissue was minced and homogenized in buffer A containing 0.4 mol L^{-1} sucrose, 1.0 mmol L^{-1} EDTA, 30.0 mmol L^{-1} Tris–HCl, 4.0 mmol L^{-1} cysteine, 0.6 % (g mL^{-1}) PVP, and 0.1 % (g mL^{-1}) BSA (pH 7.5). Then the above solution was disrupted in a Waring blender at intermediate speed for 2 min and high speed for 2 min. After centrifuged the filtrate at 1,500*g* for 10 min, the mitochondria were collected by centrifuging the supernatant at 11,000*g* for 8 min. The purification of rice mitochondria was conducted by resuspending the mitochondria in about 50 ml buffer B containing 0.3 mol L^{-1} sucrose, 1.0 mmol L^{-1} EDTA, and 10.0 mmol L^{-1} Tris–HCl (pH 7.5); the thick mitochondria were then gained. The collection was further redistributed in buffer contained 0.3 mol L^{-1} sucrose, 0.3 mol L^{-1} mannitol, and 50 mmol L^{-1} Tris–HCl (pH 7.5). And finally, the supernatant was centrifuged at 11,000*g* for 6 min. The purification of mitochondria was repeated for two times with same procedure as described above. All the above operations were performed aseptically at 0-4 °C. Mitochondrial protein was determined by Bradford method (Gornall et al. 1949).

Mitochondrial Swelling Measurement

Mitochondrial swelling was determined by monitoring the absorbance at 540 nm for 400 s at room temperature (Xia et al. 2013). Mitochondria were suspended in 2 mL buffer C containing 0.3 mol L^{-1} sucrose, 20 mmol L^{-1} HEPES, 2 mmol L^{-1} $MgCl_2$, 5 mmol L^{-1} KH_2PO_4, 20 mmol L^{-1} succinate, and 1 μmol L^{-1} rotenone (pH 7.2). The data were recorded with MAPADA UV-61 100PC double beam spectrophotometer.

To detect the permeabilization to H^+ and K^+ of mitochondrial inner membrane, potassium acetate and potassium nitrate medium were used, respectively (Fernandes et al. 2006). The potassium acetate medium contained 135 mmol L^{-1} K-acetate, 5 mmol L^{-1} HEPES, 0.1 mmol L^{-1} EGTA, 0.2 mmol L^{-1}

EDTA, 1 μg mL^{-1} valinomycin, and 2 μmol L^{-1} rotenone (pH 7.1), while the potassium nitrate medium contained 135 mmol L^{-1} KNO_3, 5 mmol L^{-1} HEPES, 0.1 mmol L^{-1} EGTA, 0.2 mmol L^{-1} EDTA, and 2 μmol L^{-1} rotenone (pH 7.1).

The effects of CsA, ADP, DTT, and MBM^+ on mitochondrial swelling were also detected to clarify the possible interaction sites of high concentration of Er(III) on rice mitochondria (Zhao et al. 2013).

Transmembrane Potential Measurement

Mitochondrial transmembrane potential ($\Delta\Psi$m) was monitored by the changes of fluorescence intensity of buffer C with Rh 123 act as the probe using LS-55 fluorophotometer (Perkin-Elmer, Norwalk, USA). The excitation and emission wavelengths were set as 488 nm and 530 nm, respectively. During the experiment, mitochondria were firstly dispersed in 2 mL buffer C containing 100 nmol L^{-1} Rh 123 at 25 °C for 10 min, then Er(III) was injected into the medium and the fluorescence intensity was recorded 5 min later (Xia et al. 2013).

Membrane Fluidity Assessment

Membrane fluidity was assessed by the fluorescence excitation anisotropy changes of HP-labeled mitochondria (Ricchelli et al. 1999). Mitochondria were dispersed in 2 mL buffer C with HP solution prepared in absolute ethanol. Anisotropic changes for HP were recorded by LS-55 fluorophotometer with the excitation and emission wavelength of 520 nm and 626 nm, respectively. The anisotropy r is defined by the following equation:

$$r = (I_{II} - GI_{\perp})/(I + 2GI_{\perp}), \quad (1)$$

where $I_{\prod}$ and $I_{\perp}$ are the fluorescence intensity polarized parallel and perpendicular to the vertical plane of polarization of the excitation beam, respectively. G represents the correction factor for instrumental artifacts with G equals to $I_{\prod}/I_{\perp}$ (Lakowicz 1999).

All the experiments repeated for about 5–7 times to eliminate the aberrations caused by instrument.

TEM of Mitochondria

Mitochondria with different concentrations of Er(III) were fixed in 2.5 % (v/v) glutaraldehyde in 0.1 mmol L^{-1} cacodylate buffer for 45 min at 4 °C, then postfix with 1 % osmium tetroxide and dehydrated (Gzyl et al. 2009). The ultra-structure of mitochondria was observed on a JEM-100CX TEM (JEOL, Tokyo, Japan).

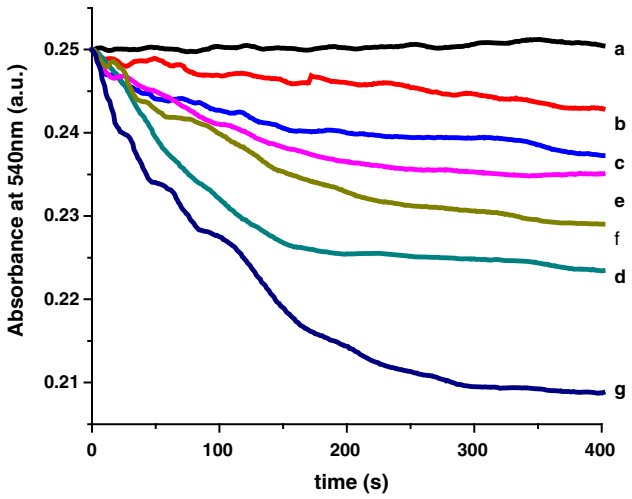

Fig. 1 Swelling of isolated rice mitochondrial caused by different concentrations of Er(III). *c* (Er(III))/μmol L^{-1}, *a–g* 0, 50, 100, 200, 300, 400, 500

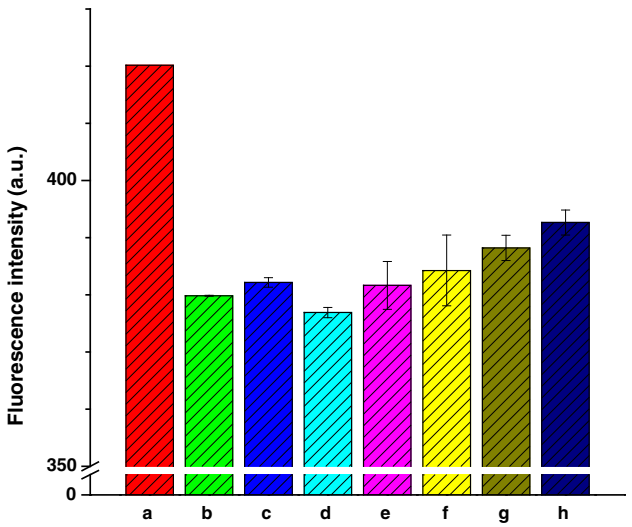

Fig. 2 Measurements of mitochondrial membrane potential ($\Delta\Psi_m$), with Rh 123 act as the probe. *Column a* was the $\Delta\Psi_m$ with only 100 nmol L^{-1} Rh123. *Column b–h* represented the $\Delta\Psi_m$ after the addition of different concentrations of Er(III), *c* (Er(III))/μmol L^{-1}: 0, 50, 100, 200, 300, 400, 500

Results

The effects of different concentrations of Er(III) on rice mitochondrial swelling were evaluated by detecting the decrease of ultraviolet absorbance values at 540 nm. As can be seen from Fig. 1, different concentrations of Er(III) could induce different degrees of mitochondrial swelling. When the concentration of Er(III) was in the range of 0–100 μmol L^{-1}, the mitochondrial swelling was unobvious; while with the increase of Er(III) concentration, the

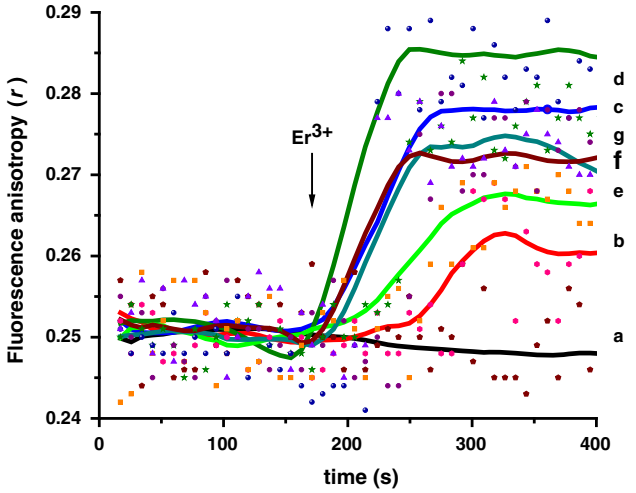

Fig. 3 Changes of mitochondrial membrane fluidity caused by different concentrations of Er(III), *c* (Er(III))/μmol L^{-1}; *a–g* 0, 50, 100, 200, 300, 400, 500

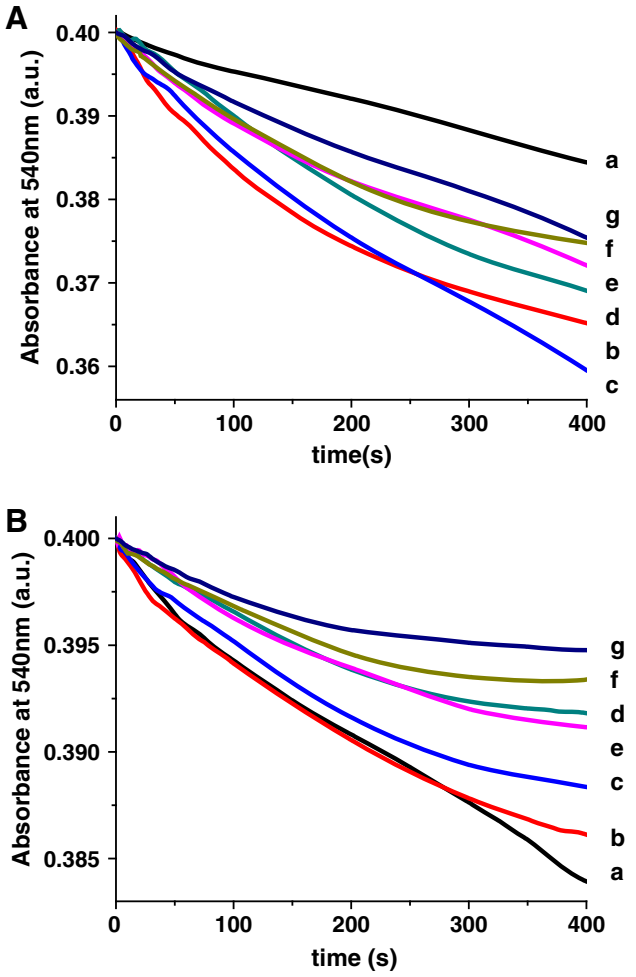

Fig. 4 Mitochondrial inner membrane permeabilization to H^+ (**a**) and K^+ (**b**) caused by different concentrations of Er(III). *c* (Er(III))/μmol L^{-1}: *a–g* 0, 50, 100, 200, 300, 400, 500

mitochondrial swelling increased gradually, especially when the concentration of Er(III) reached 500 μmol L^{-1}, the absorbance intensity was sharply declined from 0.25 to nearly 0.21, implied that the swelling was remarkable.

Mitochondrial transmembrane potential ($\Delta\Psi_m$) was evaluated by the fluoresce change of buffer C with Rh123 act as the probe. Rh123 was kind of a lipophilic cation which could accumulate in the rice mitochondrial matrix, causing the fluorescence quenching of the buffer solution. If the transmembrane potential collapse, Rh123 would release into the medium from mitochondrial matrix, which would in turn induce the increase of fluorescence intensity (Zhu et al. 2002). As shown in Fig. 2, the fluorescence intensity changed with the addition of different concentrations of Er(III) when comparing with that of column b. The intensity change was unobvious when the added Er(III) was in the concentration range of 50–200 μmol L^{-1}; while the intensity increased remarkable after the addition of Er(III) in the concentration range of 300–500 μmol L^{-1}. The above experimental phenomenon demonstrated that the addition of Er(III) with high concentration could induce the collapse of mitochondrial transmembrane potential.

The swelling of mitochondria often accompanied with the mitochondrial membrane fluidity changes (Ricchelli et al. 2005). To detect whether Er(III) has influences on rice mitochondrial membrane fluidity, the fluorescence anisotropy of mitochondria-bound HP was evaluated. As can be seen from Fig. 3, the fluorescence anisotropy raised notably when the added Er(III) concentration increased from 50 to 200 μmol L^{-1}; while when the concentration of Er(III) increased to 300 μmol L^{-1}, the fluorescence anisotropy suddenly decreased (curve e); and with the further increase of Er(III) concentration (400 and 500 μmol L^{-1}), the fluorescence anisotropy maintained at substantially the same level of that of curve e. The increase of polarization indicating that Er(III) decreased the mitochondrial membrane fluidity (Ricchelli et al. 1999).

The influence of Er(III) on mitochondrial inner membrane permeabilization to H^+ was evaluated by the de-energized mitochondria swelling. The protonated acetic acid could be transported across the inner membrane, dissociate into H^+ and acetate anion inside the mitochondria to produce an immediate proton gradient (Fernandes et al. 2006). This gradient creates a membrane potential that allows efficient phosphorylation of ADP, producing enough ATP to support for K^+ entering into mitochondria (Vercesi et al. 1991). As shown in Fig. 4a, the mitochondria underwent a valinomycin-dependent swelling with the addition of Er(III), suggesting that Er(III) promoted the membrane permeability to H^+. But with the increase of

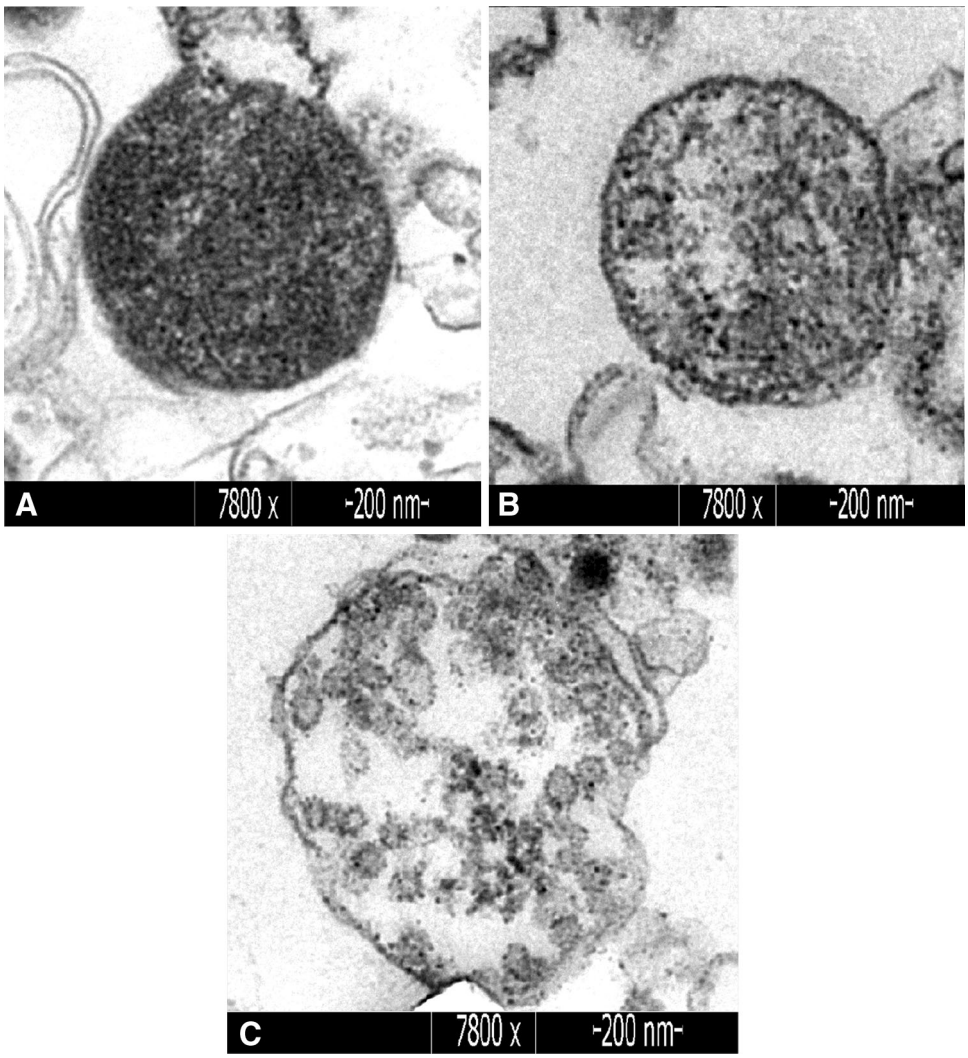

Fig. 5 TEM images of the ultra-structure of rice mitochondria incubated with Er(III) of 0 μmol L^{-1} (**a**), 100 μmol L^{-1} (**b**), and 500 μmol L^{-1}(**c**)

Er(III) concentration, the effect of promotion slowed down a bit.

Mitochondrial inner membrane permeabilization to K^+ was also evaluated by the de-energized mitochondria swelling (Fig. 4b). The protonated nitrate medium mitochondrial inner membrane is permeable to nitrate (NO_3^-), optimal swelling is observed only in conditions of K^+ permeabilization (Vicente et al. 1998). The testing results in Fig. 4b showed that the swelling decreased slowly with the increase of Er(III) concentration, demonstrating that Er(III) restrained inner membrane permeabilization to K^+.

The above experimental phenomenon and analytical results (swelling of the rice mitochondria, collapse of mitochondrial transmembrane potential, decrease of membrane fluidity, change of the permeability to H^+ and K^+) implied that Er(III) could induce MPT. In order to verify the occurrence of MPT, the ultra-structure of rice mitochondria treated with different concentrations of Er(III) was observed by TEM. As can be seen from Fig. 5a, the normal isolated rice mitochondria maintain their integrity, which contain a well-defined outer membrane, a narrow inter-membrane space, and a compact cristae. With 100 μmol L^{-1} Er(III) loaded, the ultra-structure of mitochondria was some similar to the normal one except for the hardly distinguished cristae (Fig. 5b). However, when the loading amount of Er(III) increased to 500 μmol L^{-1}, mitochondria swelled with the appearance of a large inter-membrane space and the cristae clusters underwent a remarkably volume expansion (Fig. 5c).

Four different protective agents CsA, ADP, DTT, and MBM^+ were further employed to make clear the possible reasons of rice MPT induced by Er(III). As can be seen from Fig. 6, 500 μmol L^{-1} Er(III) could induced MPT (curve b), but CsA could not suppress the mitochondrial

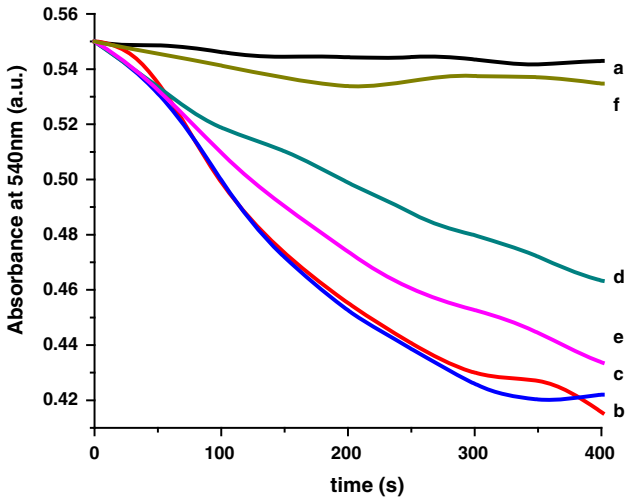

Fig. 6 Protective effect of CsA, ADP, DTT and MBM^+ on mitochondrial swelling caused by 500 μmol L^{-1} Er(III). Mitochondria untreated with Er(III) (*a*), mitochondria treated with 500 μmol L^{-1} Er(III) (*b*). Trace *c*–*f*: 500 μmol L^{-1} Er(III) with different protective of 60 μmol L^{-1} CsA (*c*), 250 μmol L^{-1} ADP (*d*), 10 μmol L^{-1}DTT (*e*), 10 μmol L^{-1} MBM^+ (*f*)

swelling caused by 500 μmol L^{-1} Er(III) (curve c), indicating that CsA did not have protective effect of mitochondrial swelling.

However, after the addition of 250 μmol L^{-1} ADP to mitochondria, the rate of UV absorbance descent cause by 500 μmol L^{-1} Er(III) was slower (curve d) when comparing to that of without ADP (curve b). This suggested that ADP protected mitochondria from swelling. Curves e and f in Fig. 6 showed that both 10 μmol L^{-1} DTT and 10 μmol L^{-1} MBM^+ could prevent the mitochondrial swelling.

Discussion

In "Results" section part, the specific experimental phenomenon of Er(III) affected mitochondrial swelling, transmembrane potential, membrane fluidity, and membrane permeability to H^+ and K^+ has been described detailedly, and in this part, the specific reasons that induced the mentioned phenomenon would be deeply analyzed and discussed.

Firstly, Er(III) could induce mitochondrial swelling. If MPT happened, mitochondria would undergo a sudden increase of permeability to solutes with molecular mass equal to or less than 1,500 Da, while proteins would remain in the matrix. As a consequence, the colloidal osmotic pressure would increase and the mitochondria would swell, which might further induce the dysfunction of mitochondria (Halestrap et al. 2004; Di Lisa and Bernardi 2006; Crompton 1999; Gerencser et al. 2008; Tang et al. 2005). As can be seen from Fig. 1, the absorbance intensity of mitochondria at 540 nm all decreased after the addition of different concentrations of Er(III), suggesting that the matrix of mitochondria expanded and the rice mitochondria swelled.

Secondly, Er(III) could collapse the mitochondrial transmembrane potential. With expansion of the mitochondrial matrix and increase of osmotic pressure, the potential gradients across the membrane collapse. Electrochemical potential gradient was regarded as a major indication of physiological conditions (Pacelli et al. 2011; Ferguson-Miller and Sorgato 1982). The collapse of transmembrane potential was regarded as the rearrangement of inner membrane from the native to random structures (Zischka et al. 2008). The phenomenon shown in Fig. 2 indicated that Er(III) depolarized mitochondrial membrane, causing the dysfunction of rice mitochondria.

Thirdly, Er(III) could decrease the mitochondrial membrane fluidity. It has been demonstrated that HP can accumulate in very polar-specific localized lipid regions, such as some of the protein regions in the inner mitochondrial membrane (Ricchelli et al. 1995). When the matrix volume expanded, the inner membrane cristae would unfold, and the modification of some protein conformation could cause the change of membrane fluidity. Er(III) decreased the membrane fluidity, as shown in Fig. 3, which indicated that Er(III) could induce the conformational variation of proteins in the mitochondrial inner membrane and lead to the dysfunction of rice mitochondria.

Moreover, Er(III) could change the membrane permeability to H^+ and K^+. H^+ and K^+ are the crucial ions that exist in the interior of cell. As reported, the opening of mitochondria K_{ATP} has three effects on mitochondrial physiology: (i) an increase in matrix volume; (ii) a mild acceleration of respiration; and (iii) a slight but significant increase in reactive oxygen species (ROS) production (Garlid and Paucek 2003; Andrukhiv et al. 2006; Costa et al. 2006). It suggests that K^+ could keep the function of mitochondria at a normal range. However, Er(III) restrained the membrane permeability to K^+ and promoted membrane permeability to H^+, as have been demonstrated by the results obtained from Fig. 4b, a, respectively, which indicated Er(III) changed the normal biological microenvironment of mitochondria.

The ultra-structure changes of mitochondria observed by TEM offered further insights into the MPT induced by Er(III). After the interaction of Er(III) with mitochondria, the outer membrane of rice mitochondria disrupted and the inner matrix volume increased, and the most obvious

change emerged when the concentration of Er(III) reached 500 μmol L^{-1} (Fig. 5).

All the above experimental analysis and discussion demonstrated that Er(III) could induced the MPT and the dysfunction of rice mitochondria. Considering that mitochondria play essential roles on respiration and metabolism, we speculated that Er(III) may have some influence on rice growth and development.

In order to clarify how Er(III) effect MPT, some important inhibitors (CsA, ADP, DTT, and MBM^+) have been employed to monitor the mitochondrial swelling of Er(III)-treated mitochondria.

Many researchers considered matrix space protein cyclophilin D (CyP-D) and adenine nucleotide translocator (ANT) located at the inner mitochondrial membrane are two important parts of a mega-channel named mitochondrial permeability transition pore (mtPTP). It has been demonstrated that CsA could interact with CyP-D to restrain mitochondrial swelling (Arpagaus et al. 2002). The evidence showed that ADP could inhibit the mtPTP open by controlling the conformation of ANT (Haworth and Hunter 2000; Majima et al. 1995; Klingenberg 2008). The experimental results that mitochondria swelling could inhibited by ADP other than CsA obtained from Fig. 6 implied that the process of Er(III) entered the mitochondria was a special MPT. DTT and MBM^+ were both thiol reagents, which could inhibit the oxidation of thiol groups of proteins that located in the mitochondrial inner membrane and block the mitochondrial swelling (Zhang et al. 2011; Kosower et al. 1979). The results presented by Fig. 6 indicated that DTT and MBM^+ could both inhibit the mitochondrial swelling. From the above analysis, it became clear that the thiol chelation mechanism was of great importance in Er(III) inhibitory action on mitochondrial swelling (Hu et al. 2006).

Conclusion

According to the above experimental analysis and discussion, it showed that Er(III) could induce the swelling of rice mitochondria, collapse of membrane potential, decrease of mitochondrial fluidity, change of the membrane permeability to H^+ and K^+, and alteration of mitochondrial ultra-structure. These further indicated that Er(III) could effect MPT and induce the dysfunction of rice mitochondria. The thiol chelation on the mitochondrial inner membrane should be the main reason that Er(III) caused the MPT phenomenon. We sincerely hope that our research work can provide some references for the understanding of the biological noxious effects of heavy REEs on rice mitochondria.

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