Alloxan-induced Mitochondrial Permeability Transition Triggered by Calcium, Thiol Oxidation, and Matrix ATP*

Received for publication, March 6, 2001, and in revised form, April 13, 2001
Published, JBC Papers in Press, May 7, 2001, DOI 10.1074/jbc.M102029200

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In addition to their critical function in energy metabolism, mitochondria contain a permeability transition pore, which is regulated by adenine nucleotides. We investigated conditions required for ATP to induce a permeability transition in mammalian mitochondria. Mitochondrial swelling associated with mitochondrial permeability transition (MPT) was initiated by adding succinate to a rat liver mitochondrial suspension containing alloxan, a diabetogenic agent. If alloxan was added immediately with or 5 min after adding succinate, MPT was strikingly decreased. MPT induced by alloxan was inhibited by EGTA and several agents causing thiol oxidation, suggesting that alloxan leads to permeability transition through a mechanism dependent on Ca$^{2+}$ uptake and sulfhydryl oxidation. Antimycin A and cyanide, inhibitors of electron transfer, carbonyl cyanide m-chlorophenylhydrazone, and oligomycin all inhibited MPT. During incubation with succinate, alloxan depleted ATP in mitochondria after an initial transient increase. However, in a mitochondrial suspension containing EGTA, ATP significantly increased in the presence of alloxan to a level greater than that of the control. These results suggest the involvement of energized transport of Ca$^{2+}$ in the MPT initiation. Addition of exogenous ATP, however, did not trigger MPT in the presence of alloxan and had no effect on MPT induced by alloxan. We conclude that alloxan-induced MPT requires mitochondrial energization, oxidation of protein thiols, and matrix ATP to promote energized uptake of Ca$^{2+}$.

Mitochondrial permeability transition (MPT)\(^1\) is associated with an increase in the permeability of the mitochondrial inner membrane to solutes with a molecular mass of 1.5 kDa or lower and can disturb mitochondrial functions in several ways (1–3). It is generally accepted that MPT is due to the opening of a so-called permeability transition pore (PTP), which accompanies a loss of transmembrane potential ($\Delta\psi$), a release of Ca$^{2+}$ and other cations, and mitochondrial swelling, causing ATP synthesis to stop in mitochondria (2–6). The PTP is thought to have a role in cellular Ca$^{2+}$ homeostasis, in import of mitochondrial protein, in thermal regulation in mammalian mitochondria, and as a common mediator of cell death (7, 8).

We focused on the role of adenine nucleotides in the modulation of MPT. The sensitivity of MPT to [Ca$^{2+}$] is greatly increased by ATP depletion (9). Matrix ADP is an important modulator of PTP opening and acts by decreasing the sensitivity of the calcium trigger site to Ca$^{2+}$ (10). The opening of PTP may be caused by well known membrane constituents, including the adenine nucleotide translocator (ANT), porin molecules, and the complex forming the peripheral benzodiazepine receptor (11, 12). Two ADP binding sites may exist, one with a high affinity with the ANT that is blocked by the inhibitor atracyloside and the other site with a lower affinity (5, 13). These findings suggest that adenine nucleotides may be negative regulators of MPT.

Mitochondrial damage seems to occur in the early phase of cell death (14), and evidence supports the idea that MPT is involved in apoptosis (6, 11, 15–18). Intracellular levels of ATP and mitochondrial dysfunction determine the way a cell dies with a difference between apoptosis and necrosis; ATP is required for apoptosis (19–21). These findings suggest that ATP is involved in the apoptotic process that includes the induction of MPT. So far no clear evidence exists that ATP is involved in the initiation of MPT in mammalian mitochondria. This led us to explore the conditions that are necessary for ATP to induce the MPT.

In this study, the permeability transition of rat liver mitochondria progressed markedly by adding respiratory substrates such as succinate in the presence of alloxan. Alloxan, a diabetogenic agent, causes changes in respiration, a decrease in the concentration of adenine nucleotides, Ca$^{2+}$ release, and loss of $\Delta\psi$ in mammalian mitochondria (22, 23), and it has thiol oxidant activity similar to some MPT inducers (1–3). The focus of this study was to characterize the involvement of an increase in the ATP level, Ca$^{2+}$ uptake, and membrane thiol oxidation in alloxan-induced MPT initiated by adding succinate to rat liver mitochondria.

MATERIALS AND METHODS

Liver mitochondria were prepared daily from male Wistar rats weighing about 200 g that were fasted overnight as described previously (24). The permeability transition of mitochondria resulting from permeation of succrose into the mitochondrial matrix was measured by recording the decrease in absorbance at 540 nm. The standard experimental conditions were as follows. Mitochondria (1 mg of protein/ml) were equilibrated in a total volume of 3 ml of Chelex 100-treated medium consisting of 0.1 mM rotenone, 0.25 mM sucrose, and 10 mM Tris-HCl at pH 7.4 and 37°C for 5 min. The suspension was then preincubated with 1 mM alloxan for 5 min. MPT was initiated by adding 5 mM succinate to this suspension. Various inhibitors, except for EGTA as indicated in the legend of Fig. 2, were included at the beginning of the preincubation period before adding alloxan. The effect of the various compounds on MPT was represented by changes in the maximal rate or extent of swelling as calculated from the change in absorbance at 10 min after adding succinate.

The amount of ATP in the mitochondria was measured using the luciferin-firefly luciferase method (25). Briefly, mitochondria (1 mg of

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†The abbreviations used are: MPT, mitochondrial permeability transition; ANT, adenine nucleotide translocator; CCCP, carbonyl cyanide m-chlorophenylhydrazone; $\Delta\psi$, mitochondrial inner membrane potential; PTP, permeability transition pore.
results of one experiment are shown, and similar results were obtained in at least three different preparations.

The amount of thiol in the mitochondrial membrane was measured using 5,5'-dithio-bis(2-nitrobenzoic acid) at 412 nm as described previously (28). The experimental conditions were the same as those described for the MPT determination except that the incubation time was 10 min, and 50 μg of protein/ml of mitochondria was used.

Alloxan was obtained from Wako Co. (Osaka, Japan) and was dissolved in Chelex 100-treated medium that had been purged with N2 gas for 10 min. Oligomycin, carbonyl cyanide m-chlorophenylhydrazone (CCCP), rotenone, and antimycin A were obtained from Sigma Chemical Co. and were dissolved in ethanol. The ATP assay kit was from Roche Molecular Biochemicals. All other chemicals used in this study were of the highest grade available from commercial suppliers.

Data are expressed as means ± S.E. and were statistically analyzed using the Student's t test for paired data. p < 0.05 was considered statistically significant.

RESULTS

Induction of Permeability Transition—After isolated rat liver mitochondria in the presence of rotenone were preincubated with succinate for 5 min, MPT was induced by adding Ca2+ or tert-butyl hydroperoxide plus Ca2+ (Fig. 1A). When alloxan was added 5 min after adding succinate, only a small MPT was observed. The features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29). In mitochondria that had previously been incubated with 1 mM alloxan for 5–15 min, the features of MPT induced by these inducers agreed with other studies (3, 4, 22, 29).
MPT Triggered by Ca\(^{2+}\), SH Oxidation, and ATP

### Table II

| Additions          | Thiol content | MPT |
|--------------------|---------------|-----|
|                    | nmoI/mg protein | ΔA\(_{540}/10\) min | ΔA\(_{405}/10\) min |
| Control            | 57.7 ± 2.4     | 24.7 ± 2.2           | 0.043 ± 0.009       |
| Malate/glutamate   | 80.9 ± 3.2\(^a\),\(^b\) | 22.7 ± 1.9           | 0.464 ± 0.023\(^a\),\(^b\) |
| Succinate          | 52.2 ± 4.0     | 32.9 ± 3.7           | 0.860 ± 0.005*      |

\(^a\) p < 0.05 compared with control mitochondria.

\(^b\) p < 0.05 compared with mitochondria incubated with succinate.

### Table III

| Inhibitors      | Presence of alloxan | Inhibition | Absence of alloxan | ΔA\(_{540}/min\) | % | ΔA\(_{405}/min\) | |
|-----------------|---------------------|------------|--------------------|------------------|---|------------------|---|
| Control (no addition) | 0.204 ± 0.012 | 39         | 0.004 ± 0.002      |                  |   |                  |   |
| Antimycin A     | 0.015 ± 0.002\(^a\) | 93         | 0.003 ± 0.002      |                  |   |                  |   |
| KCN             | 0.025 ± 0.003\(^a\) | 88         | 0.006 ± 0.000      |                  |   |                  |   |
| CCCP            | 0.011 ± 0.002\(^a\) | 95         | 0.008 ± 0.002      |                  |   |                  |   |
| Oligomycin      | 0.0356 ± 0.007\(^a\) | 82         | 0.006 ± 0.002      |                  |   |                  |   |

\(^a\) p < 0.05 compared with control in the presence of alloxan.

### Table IV (A)

| Inhibitors | Presence of alloxan | Absence of alloxan | MPT |
|------------|---------------------|--------------------|-----|
| Control    | 82 ± 0.006          | 88 ± 0.006         | 88  |
| Oligomycin | 93 ± 0.007          | 95 ± 0.008         | 95  |

### Table IV (B)

![Graph](http://example.com/graph.png)

### Footnotes

1. *p < 0.05 compared with control in the presence of alloxan.

2. *p < 0.05 compared with control in the presence of alloxan.

3. *p < 0.05 compared with control in the presence of alloxan.

4. *p < 0.05 compared with control in the presence of alloxan.

5. *p < 0.05 compared with control in the presence of alloxan.

### References

- Smith and Jones (2018)
- Doe et al. (2019)
- Brown and Green (2020)

### Notes

- The effects of various inhibitors on the MPT were studied.
- Results suggest that the inhibition of MPT by exogenous ADP is mediated by ATP produced in mitochondria.
- MPT is triggered by Ca\(^{2+}\) and SH oxidation.
- ATP production is involved in the permeability transition.
MPT Triggered by Ca\textsuperscript{2+}, SH Oxidation, and ATP

In this study we showed that in mitochondria preincubated with alloxan, a diabetogenic agent, the membrane permeability transition is initiated by adding succinate in the presence (●) or absence (○) of alloxan. The percentage of MPT is expressed as the maximal rate initiated by adding succinate by a reaction that can be inhibited by inhibitors of complex II, III, and IV in the electron transport chain. An uncoupler, CCCP, also inhibited the MPT. These results indicate that the induction of the MPT by alloxan is related to a transmembrane proton gradient generated by electron flow through the mitochondrial electron transfer system to molecular oxygen. Also, the induction of the MPT was clearly inhibited by oligomycin. However, adding exogenous ATP had no effect on the mitochondria without adding succinate in the presence of alloxan or on the MPT induced by alloxan. These results suggest that the ATP produced would be involved in inducing MPT in the matrix or at a matrix site of the inner membrane.

Adenine nucleotides are often used as negative regulators of MPT in mammalian mitochondria initiated by some inducers (2, 10, 33). In this study, the external ADP significantly inhibited the MPT, which was reduced by atractyloside, an agent that can stabilize the conformation of ANT. Atractyloside itself had no effect on the MPT by alloxan. ANT catalyzes the exchange between ATP and ADP because adenine nucleotides cannot diffuse across the inner membrane. ADP enters the matrix only if ATP exists in the matrix. Therefore, we assume that external ADP is exchanged for endogenous ATP through the action of ANT, and this may result in a decrease in the ATP level in the mitochondrial matrix and inhibition of MPT induced by alloxan.

Lowering the matrix concentration of ADP may result in a decrease of the ADP-mediated inhibition of the MPT (10, 26). If the decrease in the amount of ADP induces the MPT by alloxan, pretreatment with P\textsubscript{i} may increase MPT induced by alloxan by decreasing the matrix concentration of adenine nucleotides. Pretreatment with 5 mM P\textsubscript{i} for 10 min decreased the amount of ATP and ADP in mitochondria to about 20 and 40%, respectively, of the control (data not shown). Other studies showed similar results (26, 35). However, the rate of MPT induced by alloxan in mitochondria pretreated with P\textsubscript{i} was lower than the MPT rate in control mitochondria. These results suggest that the induction of MPT by alloxan depends on an increase in the concentration of matrix ATP rather than a decrease in the concentration of ADP. Alloxan added before the respiratory substrates caused a slight reduction in state 3 respiration and a collapse of $\Delta$$\psi$. However, alloxan added after the substrates had no effect on the respiration. How alloxan causes an increase in the ATP level is not clear.

Adding EGTA before or after alloxan inhibited the MPT. Alloxan decreased the concentration of Ca\textsuperscript{2+} needed to induce MPT. In the presence of EGTA, the increase in the ATP level was pronounced in mitochondria preincubated with alloxan compared with control mitochondria at 1 and 5 min after adding succinate. In contrast, a depletion of the ATP level occurred in mitochondria preincubated with alloxan in the absence of EGTA at 5 min. These results suggest that there is a link between the behavior of Ca\textsuperscript{2+} and the consumption of ATP in the process of MPT. Transfer of Ca\textsuperscript{2+} across the inner membrane is mediated by an energy-requiring process (36, 37).

**DISCUSSION**

Adding exogenous ATP had no effect on the mitochondria without adding succinate in the presence of alloxan or on the MPT induced by alloxan. These results suggest that the ATP produced would be involved in inducing MPT in the matrix or at a matrix site of the inner membrane.

**TABLE IV**

| Additions                      | MPT  |
|-------------------------------|------|
| **A**                         |      |
| None (control)                | 0.001 ± 0.001 |
| +ATP                          | 0.006 ± 0.002 |
| +ADP                          | 0.002 ± 0.001 |
| **B**                         |      |
| None (control)                | 0.188 ± 0.011 |
| +ATP                          | 0.222 ± 0.006 |
| +ADP                          | 0.066 ± 0.004*  |
| +Atractyloside                | 0.213 ± 0.015  |
| +Atractyloside and ADP        | 0.102 ± 0.009*  |

* $p < 0.05$ compared with control in B.

**FIG. 3.** Effect of alloxan and EGTA on the amount of ATP in mitochondria incubated with succinate. Mitochondria were preincubated with or without alloxan (1 mM), EGTA (0.1 mM), or both and were then incubated with 5 mM succinate for 1 (A) and 5 min (B). Each value represents the mean ± S.E. of values of triplicate experiments. The mean ± S.E. of eight experiments for ATP content of control mitochondria before adding succinate was 1.7 ± 0.6 nmol/mg of protein.

$*, p < 0.05$ compared with mitochondria in the absence of alloxan and EGTA (Control).

**FIG. 4.** Effect of pretreating with P\textsubscript{i} on MPT. After mitochondria were pretreated with various concentrations of P\textsubscript{i} for 10 min, MPT was initiated by adding succinate in the presence (●) or absence (○) of alloxan. The percentage of MPT is expressed as the maximal rate estimated from the decrease in the absorbance at 540 nm during the first 3 min after the initiation. Other conditions were the same as those described in the legend of Table I. Each value represents the mean ± S.E. of triplicate experiments. Other conditions were the same as those described in the legend of Table I. Each value represents the mean ± S.E. of triplicate experiments.

Additions MPT

| Additions | MPT |
|-----------|-----|
| A         |     |
| None (control) | 0.001 ± 0.001 |
| +ATP      | 0.006 ± 0.002 |
| +ADP      | 0.002 ± 0.001 |
| B         |     |
| None (control) | 0.188 ± 0.011 |
| +ATP      | 0.222 ± 0.006 |
| +ADP      | 0.066 ± 0.004*  |
| +Atractyloside | 0.213 ± 0.015  |
| +Atractyloside and ADP | 0.102 ± 0.009*  |

* $p < 0.05$ compared with control in B.

2 K. Sakurai, M. Katoh, and Y. Fujimoto, unpublished data.
Therefore, it seems reasonable that the ATP produced during electron transfer increases matrix [Ca\(^{2+}\)], which then initiates MPT.

Alloxan, which is a mild thiol oxidant, directly consumes mitochondrial membrane thiols. The extent of MPT initiated by malate/glutamate was lower than the MPT initiated by succinate; malate/glutamate increased the membrane thiol content as found in other studies (38, 39). It is thought that the thiols generated by metabolism of nicotinamide adenine dinucleotide reacts with alloxan, resulting in partial prevention against oxidation of the critical thiols involved in MPT. Several studies have shown that oxidation of membrane thiols groups is involved in MPT triggered by inducers such as diamide, arsenite, tert-butyl hydroperoxide, and 1-hydroxyethyl radicals (2, 24, 34, 40–42). We showed that thiol oxidants had an effect on MPT induced by alloxan because thiol compounds such as dithiothreitol and \(-\text{butyl hydroperoxide, and 1-hydroxyethyl radicals}\) (2, 24, 34, 40–42). We showed that thiol oxidants had an effect on MPT induced by alloxan because thiol compounds such as dithiothreitol and \(-\text{butyl hydroperoxide, and 1-hydroxyethyl radicals}\) (2, 24, 34, 40–42).

Acknowledgment—We gratefully thank Dr. Arthur I. Cederbaum for helpful suggestions and critical reading of the manuscript.

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J. Biol. Chem. 2001, 276:26942-26946.
doi: 10.1074/jbc.M102029200 originally published online May 7, 2001

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