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Journal of Pharmacological Reports

Short Communication

NADH and ATP Oscillations in Mitochondria

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ABSTRACT

Oscillations of mitochondrial intermediates were investigated based on the idea that enzymatic oscillatory reactions are caused by the permeation of substrate through membrane. We found that both NADH and ATP oscillate in mitochondria as pyruvate enters with ADP gradually. Similarly, the gradual entry of NAD^+ and malate along with ADP also resulted in NADH and ATP oscillations. At the same time, pH oscillations in mitochondria were also observed in both cases. Compared to the model experiments using dialysis membranes, it was found that the oscillatory reaction due to the gradual entry of pyruvate was inherited by both the citric acid cycle and the respiratory chain, ultimately causing ATP oscillation in oxidative phosphorylation. Furthermore, it was found that when NAD^+ and malate were used instead of pyruvate, the oscillations of NADH and ATP occurred without going through the citric acid cycle.

Key words: ATP oscillation; NADH oscillation; Mitochondria; Membrane permeation

ABOUT THE STUDY

Mitochondria are organelles that produce ATP, a bioenergetic source. NADH is produced in the citric acid cycle and consumed in the respiratory chain. Respiratory chain is coupled to the generation of ATP by oxidative phosphorylation. Mitochondria have an outer membrane and an inner membrane that is selectively permeable, enclosing a matrix within. Electrons flow through the respiratory chain passing through three large protein complexes: NADH-Coenzyme Q (CoQ) oxidoreductase (Complex I), CoQ-Cytochrome c oxidoreductase (Complex III) and cytochrome c oxidase (Complex IV). The proton motive force drives a membrane-located ATP synthase that forms ATP in the presence of Pi+ADP. ATP synthase in embedded in the inner membrane, together with the respiratory complexes.

Based on the facts described below, it is thought that NADH and ATP oscillate in the mitochondria because the mitochondrial reaction begins with the permeation of the substrate such as pyruvate through the membrane.

It is well known that self-organizing phenomena such as oscillatory reactions appear in situations far from equilibrium [1]. The most famous chemical oscillator is the non-linear oscillating reaction, still known as the Belousov-Zhabotinsky (BZ) reaction [2]. The first observations of oscillatory behaviour in glycolysis were made in 1957 [3]. Glycolytic oscillations have been thought to be caused by allosteric enzymes [4].

We first discovered an enzymatic oscillatory reaction in the reaction of alcohol dehydrogenase using the oil/water interface [5,6]. We then used dialysis membranes to discover that many enzymes oscillate [7,8]. Gradual entry of the substrate was considered to be essential to trigger the enzymatic oscillatory reaction, and the proper combination of permeation rate through the membrane of the substrate and the rate constant of the catalytic reaction regulates the oscillation. Based on these results, we came to the idea that an oscillatory reaction also occurs in an actual living system. We confirmed that NADH and ATP oscillations actually occur using mitochondria [9].

Model experiment using dialysis membrane

Transmembrane permeation of pyruvate is required for reactions to occur in mitochondria. Pyruvate crosses the inner membrane by pyruvate transporters [10,11]. NADH produced in glycolysis is also used in the respiratory chain. However, NADH cannot permeate membranes, so it is generated intramembranely using the malate-aspartate shuttle [12]. We tried to replace these

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Received: 23-Sep-2022, Manuscript No. JPR-22-19332; **Editor assigned:** 26-Sep-2022, PreQC No: JPR-22-19332(PQ); **Reviewed:** 10-Oct-2022, QC No: JPR-22-19332; **Revised:** 17-Oct-2022, Manuscript No: JPR-22-19332 (R). **Published:** 24-Oct-2022; DOI: 10.35248/JPR.22.6.131

Citation: Hideshima T (2022) NADH and ATP Oscillations in Mitochondria. J Pharma Reports. 06:131.

membrane permeation processes with an experiment using a dialysis membrane.

A glass tube, one end covered with a dialysis membrane, was inserted into a glass cuvette containing the enzyme solution (2 mL). The substrate solution (1 mL) was placed in a glass tube. The substrate that passed through the dialysis membrane reacted in the enzyme solution. The reaction was investigated by measuring the absorbance of various intermediates.

First, NADH oscillation was observed in the reaction of pyruvate with NAD^+ and CoA by pyruvate dehydrogenase. Furthermore, when the reaction in the first stage of the citric acid cycle was added and investigated, it was found that the oscillations of NADH and cis-aconitic acid occurred at the same time in synchronization. It was suggested that the oscillations caused by the gradual entry of pyruvate cause the subsequent oscillatory reaction in the citric acid cycle.

Next, the reaction of the enzyme present in the respiratory chain was investigated. First, it was found that an oscillatory reaction occurs due to the reaction between CoQ and NADH trapped in liposomes made of phospholipids. Complex III and IV substances were added to this system one after another. It was found that NADH, which is an intermediate of the respiratory chain, and cytochrome c (reduced form) oscillate at the same time in synchronization. This indicates that the reaction of the respiratory chain is also continuously oscillating. Since the formation of NADH is gradually caused in *vivo* by the malate-aspartate shuttle, NADH oscillations are also expected to occur in the respiratory chain *via* the malate-aspartate shuttle.

Experiment using mitochondria

When the isolated mitochondria were dispersed in pyruvate solution, it was found that both NADH and ATP oscillate in mitochondria as pyruvate enters with ADP gradually. Similarly, the gradual entry of NAD^+ and malate along with ADP also resulted in NADH and ATP oscillations. With reference to experiments with dialysis membranes, we have come to the conclusions that the oscillatory reaction caused by the gradual entry of pyruvate was taken over by both the citric acid cycle and the respiratory chain, eventually resulting the oscillation of ATP in oxidative phosphorylation. When NAD^+ and malate were used instead of pyruvate, the oscillations of NADH and ATP occurred without going through the citric acid cycle. It was also observed that pH oscillations occur in both cases.

CONCLUSION

This indicates that the oscillation is inherited, and pH oscillations can cause ATP oscillations. Based on the idea that the oscillatory reaction of the enzyme caused by the membrane permeation of the substrate is taken over by the next reactions, we were really able to confirm the oscillation of NADH and ATP in mitochondria. Our findings suggest that oscillatory reactions caused by substrate permeation and subsequent continuous oscillatory reactions can occur even in many parts other than mitochondria.

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