ATP metabolism in RBC as potential biomarker for post-exercise hypotension and a therapeutic target for cardiovascular drugs

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ATP metabolism in RBC as potential biomarker for post-exercise hypotension and a therapeutic target for cardiovascular drugs

- Breakdown of ATP to AMP in the RBC is a potential biomarker for serious cardiovascular toxicity and/or mortality

- Preserving ATP in the RBC is a potential drug target for cardiovascular protection

Effect of exercise pre-conditioning on AMP concentrations in RBC in an experimental rat model of acute MI in vivo
Adenosine /ATP Transport and Metabolism
Effect of Exercise on ATP Metabolism in RBC


Treadmill exercise 15 min at a speed of 10 m/min and 5% grade
Effect of Exercise in SDR vs SHR
Yeung, P. K et al. Effect of acute exercise on cardiovascular hemodynamic and red blood cell concentrations of purine nucleotides in hypertensive compared with normotensive rats. Therapeutic Advances in Cardiovascular Disease 7(2):63-74, 2013.
Correlations between RBC [ATP] and DBP post exercise

Yeung, P. K et al. Effect of acute exercise on cardiovascular hemodynamic and red blood cell concentrations of purine nucleotides in hypertensive compared with normotensive rats. Therapeutic Advances in Cardiovascular Disease 7(2):63-74, 2013.
Effect of exercise on RBC adenine nucleotide concentrations in healthy subjects


The examined individuals were subjected to a continuous effort test with progressively increasing intensity (up to a refusal) on a cycloergometer.
Acute MI Model induced by Isoproterenol

- Isoproterenol (30 mg/kg) by sc injection
- 10 blood samples taken (0.3 mL each) for measurement of biomarkers
- 50 % mortality
Acute MI Model induced by Isoproterenol

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Effect of Cardiovascular Injury on ATP and Adenosine Metabolism in RBC


Baseline Concentrations

After Isoproterenol Injection (30 mg/kg ip)
Effect of Cardiovascular Injury on ATP and Adenosine Metabolism in RBC


- Tmax of adenosine (ADO) and uric acid (UA) after isoproterenol was shorter (ca 1hr) than the Tmax of ADP and AMP after isoproterenol (ca. 2 hr)

- ADO and UA in the plasma pool were produced from other sites in addition to the RBC
Rat Model for Exercise Preconditioning Study
Effect of Exercise Pre-conditioning on Cardiovascular Hemodynamics and ATP Metabolism in RBC


LowEx = 15 min at 10 m/m and 10% grade
Mortality = 2 of 7
VigEx = 15 min at 14 m/min and 22% grade
Mortality = 2 of 8
NoEx Mortality = 5 of 10
NoIso Mortality = 0 of 10
Effect of Exercise Preconditioning (VigEx) on Cardiovascular Protection


LowEx = 15 min at 10 m/m and 10% grade
Mortality = 2 of 7

VigEx = 15 min at 14 m/min and 22% grade
Mortality = 2 of 8

NoEx Mortality = 5 of 10
NoIso Mortality = 0 of 10
Effect of Diltiazem (DTZ) on cardiovascular toxicities induced by isoproterenol


Mortality (Control) = ca 50%

Mortality (DTZ) = < 20%
Conclusions

- ATP metabolism in RBC is potential biomarker for post-exercise hypotension
- Breakdown of ATP in the RBC is a potential biomarker for serious cardiovascular toxicity and/or mortality
- Rebound of blood pressure induced by isoproterenol is a potential biomarker for serious cardiovascular toxicity
- Preserving ATP in the RBC is a potential drug target for cardiovascular protection
Challenges and Opportunities for ATP metabolism as Biomarker target

**Challenges**

- Instability of ATP and adenosine in blood samples.
- Blood samples need to be collected carefully to avoid damage to blood cells.
- Blood samples need to be processed immediately after collection using a suitable “Stopping Solution”

**Opportunities**

- Disease and health management:
  - May be a measure of “Inner Energy”, “Reserves”, and “Cardiovascular homeostasis”
  - Cardiovascular and metabolic diseases, cancer, aging, stroke and other neurodegenerated diseases.
- Drug development:
  - Cardiovascular protective agents (ARB, ACEI, CCB, rennin and thrombin inhibitor, anti-platelet agent, B-blocker, ant-coagulant, NHP, and others)
  - Anti-cancer agents and cardiovascular toxicities
  - Antibiotics and anti-inflammatory agents
- Complementary medicine:
  - Natural health products.
  - Traditional Chinese medicines
  - Energy supplements
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