# The Biochemistry of Metabolic Acidosis

Robert A. Robergs, Ph.D., FASEP, EPC

*Exercise Science Program*
*Department of Health, Exercise & Sports Sciences*
*The University of New Mexico*
*Albuquerque, NM*
*U.S.A.*

## What is an acid?

- A proton donor/molecule that will release a proton

$CH_3\text{-}COOH \Leftrightarrow CH_3\text{-}COO^- + H^+$

*Acetic acid* ⇔ *Acetate*

$CH_3\text{-}CHOH\text{-}COOH \Leftrightarrow CH_3\text{-}CHOH\text{-}COO^- + H^+$

*Lactic acid* ⇔ *Lactate*

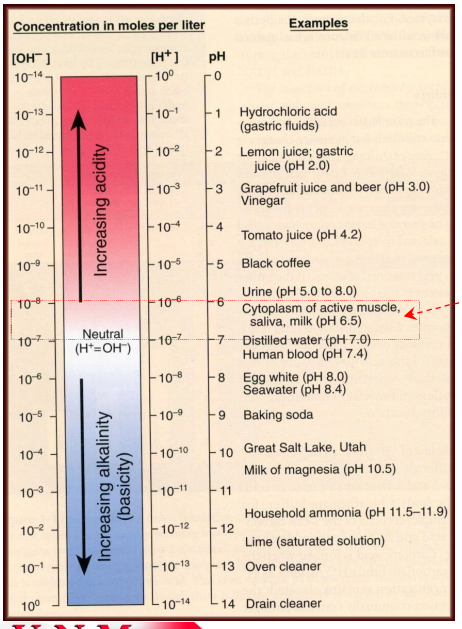
$NH_4^+ \Leftrightarrow NH_3 + H^+$

*Ammonium ion* ⇔ *Ammonia*

Do all $H^+$ released in metabolism come from acids?

**NO!**

# What is acidosis?




$pH = -\log [H^+]$

where

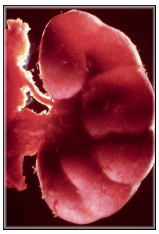
pH = 7

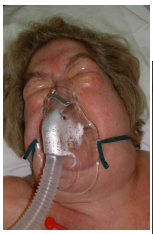
= 0.0000001 M

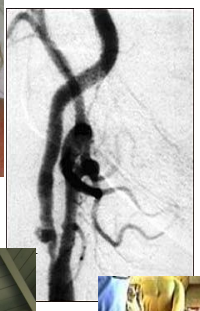
= 0.0001 mmol/L

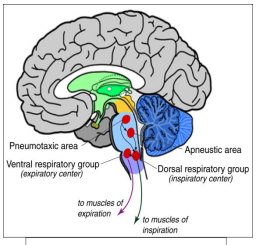
*Physiological range of cellular pH*

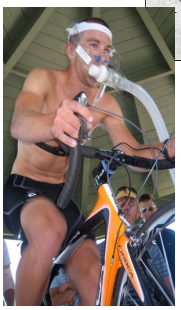
# Importance of Metabolic Acidosis

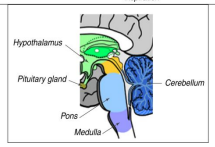










## Experimental Research Options

**Exacerbate acidosis**

- Diet
- ↓ buffering
- Hypoxia
- Anoxia
- Ischemia

**Increase buffering**

- Training
- $Na^+HCO_3^-$
- $Na^+Citrate^-$

Fatigue & Acidosis

**Intense exercise to failure**

- Wingate
- AOD
- $VO_2max$
- Max steady state
- Resistance exercise
- $^{31}P$ MRS

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## Exercise-Induced Metabolic Acidosis

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## Suggested Mechanisms

Fatigue & Acidosis

Detriment

Enzyme inhibition (partial)

↓ ATP turnover

↑ $Lactate^-$

↓ Membrane excitability

Systemic acidosis

Hyperventilation

↓ Central drive???

Benefit

↓ $K^+$ efflux

Preserve intramuscular $K^+$

Improve contractile force

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## Severe systemic acidosis induces nausea!

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## Problems Concerning Acidosis

1. We are still debating the biochemical cause of metabolic acidosis!
2. Our calculations of the muscle buffer capacity have been and remain invalid!
3. We do not know how to compute the $H^+$ load of contracting muscle during intense exercise.
4. How do we interpret evidence of improved muscle contractile function caused by acidosis?
5. Does the Stewart (Physico-chemical) theory of acid-base balance explain exercise-induced metabolic acidosis?

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## Historical Metabolic Research

A.V. Hill

1922 Nobel Prize

O. Meyerhof

L.J. Henderson

Validation of acid-base chemistry theories in 1940's

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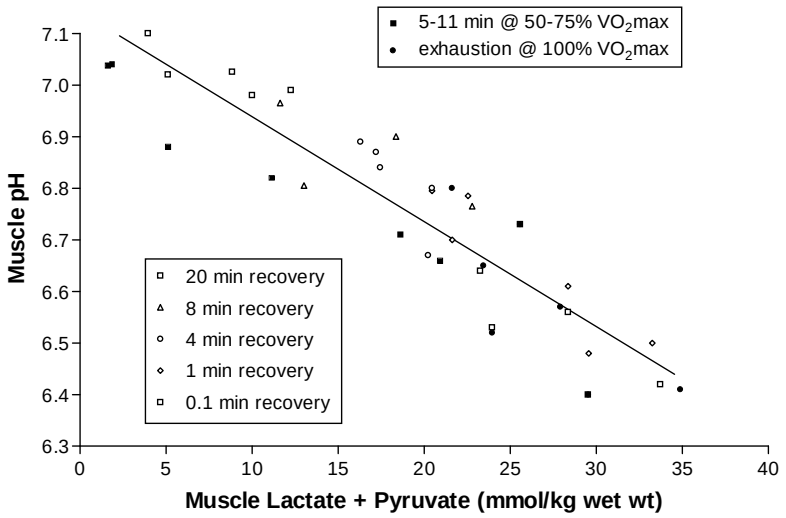
*Sahlin K et al. Pflugers Arch 367:143-149, 1976.*

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## Historical Summary

- Acid-base chemistry was not established and proven until the mid-1940's!
- The unproven concept of a lactic acidosis was developed without research evidence, without an understanding of acid-base chemistry, and was left unchallenged for almost 200 years.
- More modern scientific inquiry and interpretation (1950 – 2000) has been based on the tight correlations between lactate accumulation and muscle pH.
- Initial academic challenges to a lactic acidosis began in the 1970's.
- Lactic acidosis has been cemented as a construct in the basic, clinical and applied sciences, and remains difficult to eradicate.

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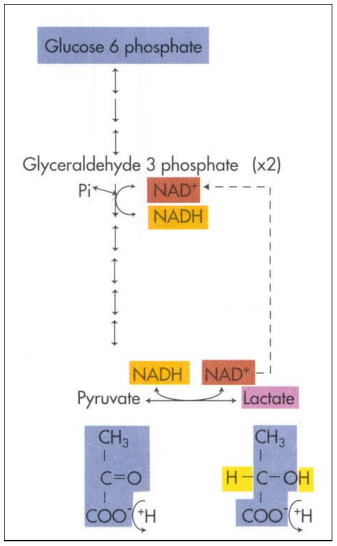
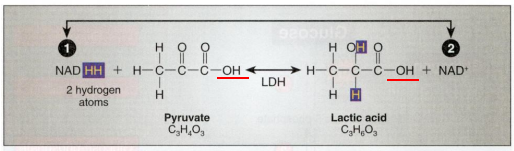
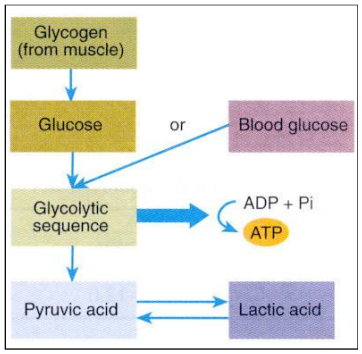
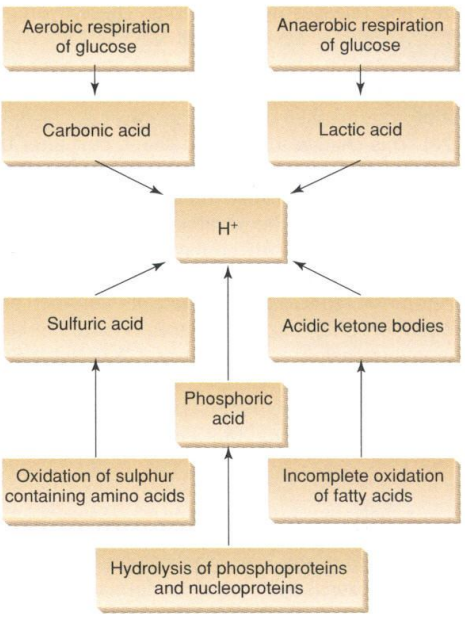
## Textbook Content



## Research Content

The terms "lactic acid" and "lactic acidosis" are still routinley used in research publications from prestigious journals!

Stringer W., Wasseman K, Casaburi R. et al., Lactic acidosis as a facilitator of oxyhemoglobin disociation during exercise. J. Appl. Physiol. 76(4):1462-1467, 1994.

- p.1462: *".....the newly formed lactic acid (pK=3.8) must be completely buffered in the cell ..... Because $HCO_3^-$ is the predominant buffer of lactic acid ....."*

- Boning D., Maassen N., Thomas A., Steinacker JM. Extracellular pH defense against lactic acid in normoxia and hypoxia before and after a Himalayan expedition. Eur. J. Appl. Physiol. 84:78-86, 2001.
- Wals B., Tiivel T., Tonkonogi M., Sahlin K. Increased concentrations of Pi and lactic acid reduce creatine-stimulated respiration in muscle fibers. J. Appl. Physiol. 92(6):2273-2276, 2002.

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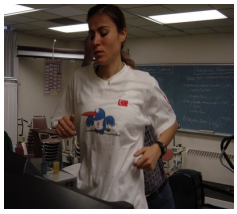
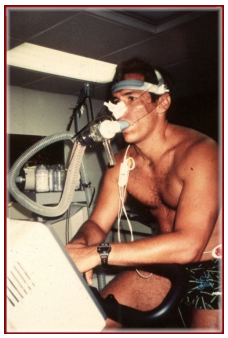
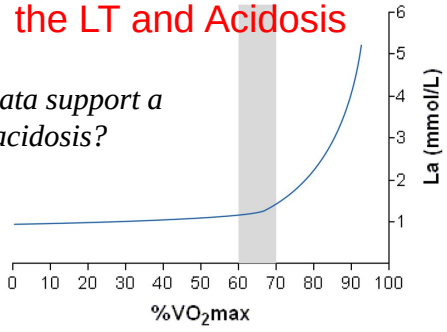
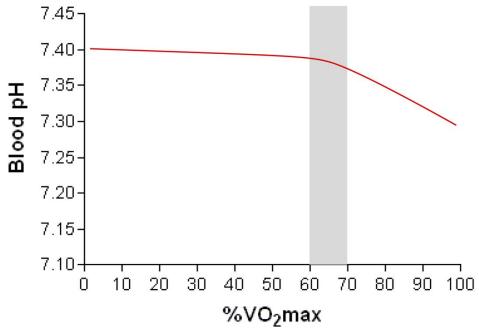
## Blood Lactate Accumulation, the LT and Acidosis





*Does this data support a lactic acidosis?*

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# Important Reactions to Proton Balance

## Glycolysis

**Table 15-2**
Reactions of glycolysis

| Step | Reaction | Enzyme | Type* | ΔG°′ | ΔG |
|---|---|---|---|---|---|
| 1 | Glucose + ATP ⟶ glucose 6-phosphate + ADP + $H^+$ | Hexokinase | a | −4.0 | −8.0 |
| 2 | Glucose 6-phosphate ⇌ fructose 6-phosphate | Phosphoglucose isomerase | c | +0.4 | −0.6 |
| 3 | Fructose 6-phosphate + ATP ⟶ fructose 1,6-bisphosphate + ADP + $H^+$ | Phosphofructokinase | a | −3.4 | −5.3 |
| 4 | Fructose 1,6-bisphosphate ⇌ dihydroxyacetone phosphate + glyceraldehyde 3-phosphate | Aldolase | e | +5.7 | −0.3 |
| 5 ↓x 2 | Dihydroxyacetone phosphate ⇌ glyceraldehyde 3-phosphate | Triose phosphate isomerase | c | +1.8 | +0.6 |
| 6 | Glyceraldehyde 3-phosphate + $P_i$ + $NAD^+$ ⇌ 1,3-bisphosphoglycerate + NADH + $H^+$ | Glyceraldehyde 3-phosphate dehydrogenase | f | +1.5 | −0.4 |
| 7 | 1,3-Bisphosphoglycerate + ADP ⇌ 3-phosphoglycerate + ATP | Phosphoglycerate kinase | a | −4.5 | +0.3 |
| 8 | 3-Phosphoglycerate ⇌ 2-phosphoglycerate | Phosphoglyceromutase | b | +1.1 | +0.2 |
| 9 | 2-Phosphoglycerate ⇌ phosphoenolpyruvate + $H_2O$ | Enolase | d | +0.4 | −0.8 |
| 10 | Phosphoenolpyruvate + ADP + $H^+$ ⟶ pyruvate + ATP | Pyruvate kinase | a | −7.5 | −4.0 |

Note: ΔG°′ and ΔG are expressed in kcal/mol. ΔG, the actual free-energy change, has been calculated from ΔG°′ and known concentrations of reactants under typical physiological conditions.

*Reaction type: (a) Phosphoryl transfer (b) Phosphoryl shift (c) Isomerization (d) Dehydration (e) Aldol cleavage (f) Phosphorylation coupled to oxidation

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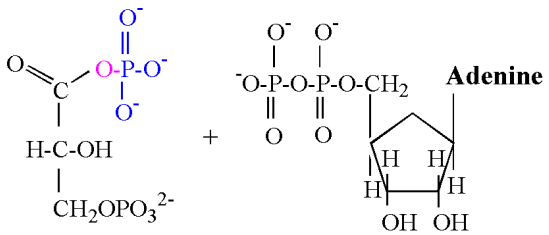
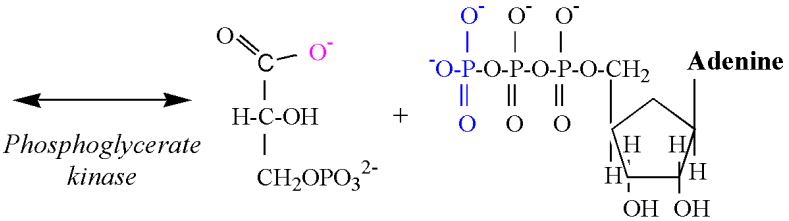
# PGK reaction does not cause a decrease in pH




1,3 Bisphosphoglycerate ADP




3-Phosphoglycerate ATP

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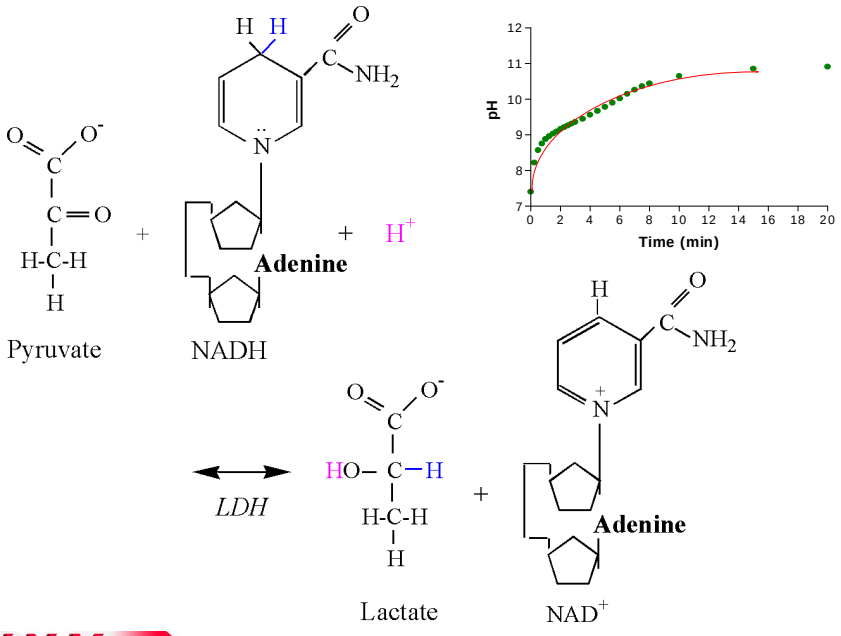
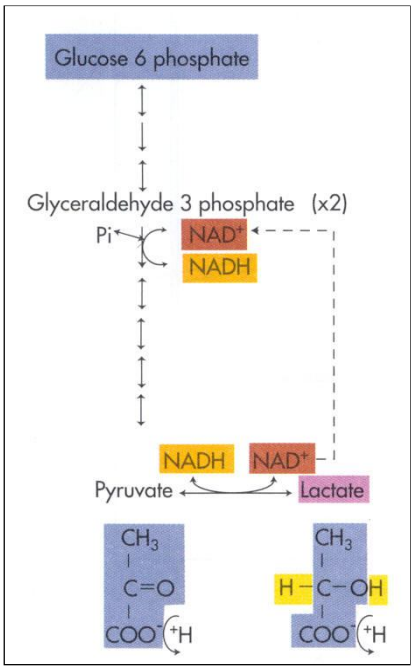
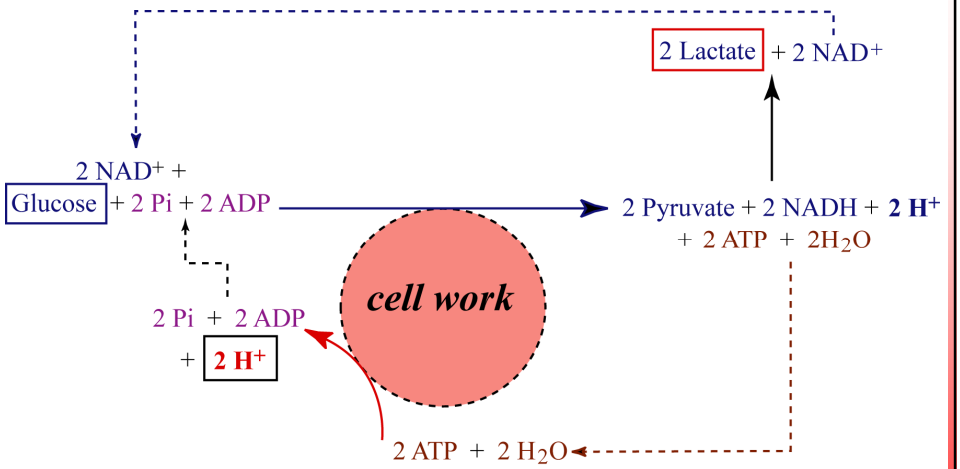
## Lactate Production



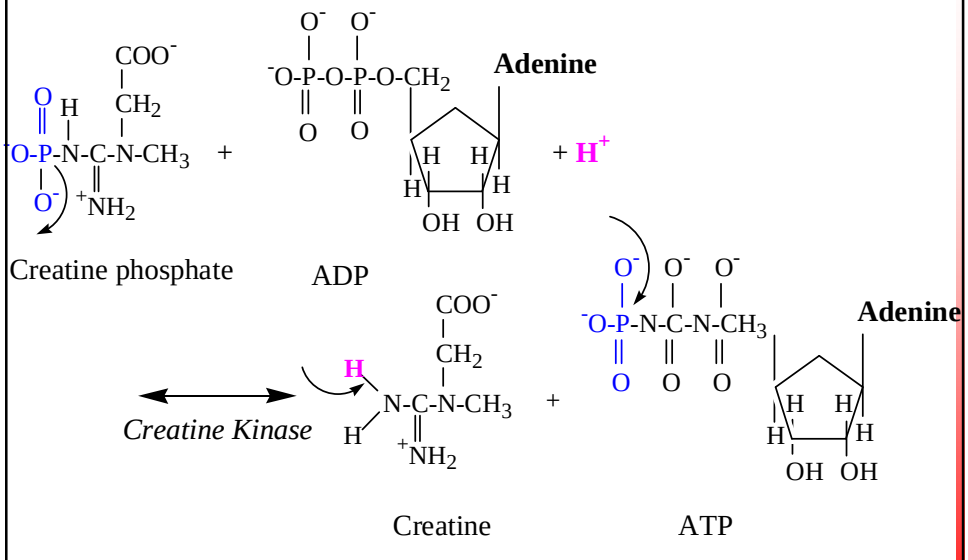

## Lactate Production Is Good For Muscle



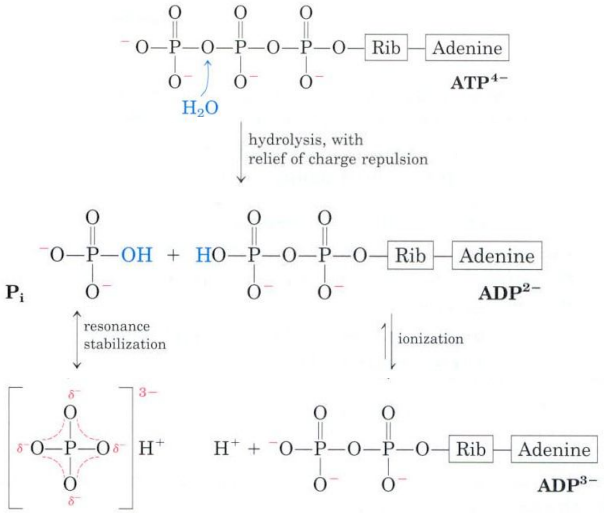
## Summary of Glycolysis and Lactate Production




## CK Reaction Consumes Protons



## ATP Hydrolysis Releases Protons

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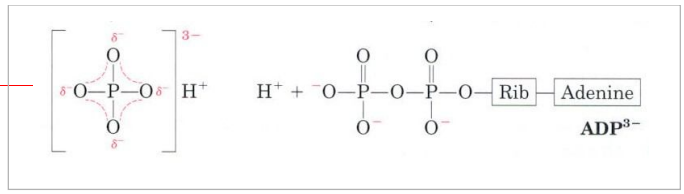
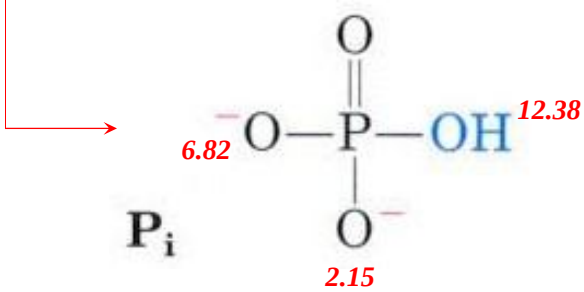
## ATP Hydrolysis, cont'd




pKa's of inorganic phosphate are:

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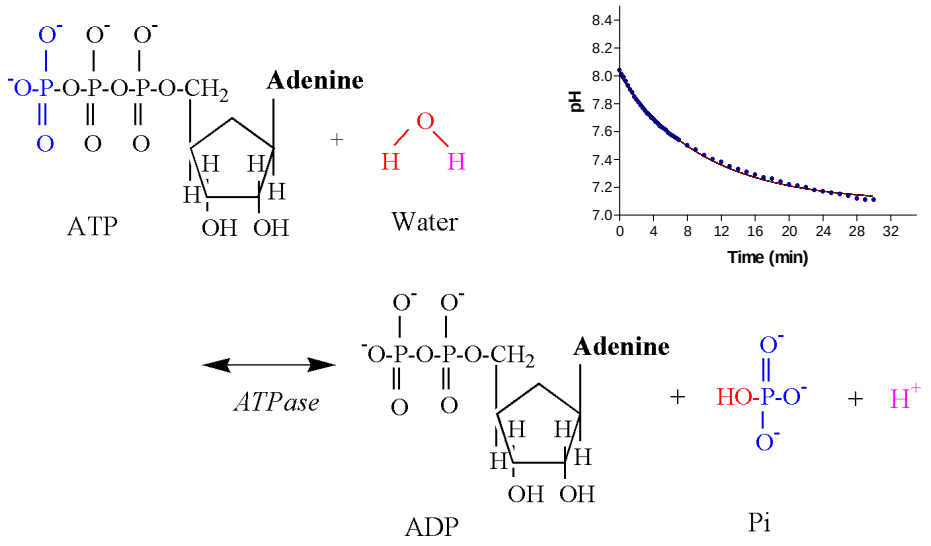
ATP Hydrolysis, cont'd

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## What causes metabolic acidosis in skeletal muscle?

Acidosis develops when the rate of $H^+$ production exceeds the rate of $H^+$ removal/buffering

| ***$H^+$ production*** | ***$H^+$ removal/buffering*** |
|---|---|
| Glycolytic flux | CrP hydrolysis |
| ATP hydrolysis | Mitochondrial transport |
| • *FT motor unit recruitment* | Proteins/amino acids |
| Proton release from reactions | $HCO_3^-$ |
| Electrolyte shifts | Inorganic phosphate |
| | Sarcolemmal transport |
| | Lactate production |

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## Conclusions

- Modeling proton load and metabolic buffering reveals the importance/validity of ATP hydrolysis as the cause of metabolic acidosis in contracting skeletal muscle.
- Controversy still exists as to the likelihood that electrolyte shifts contribute to acidosis.
- Both the LDH and CK reactions cause the initial alkalization of contracting skeletal muscle.
- Lactate production is the most important metabolic $H^+$ buffering reaction.
- If muscle did not produce lactate, we would not be able to perform intense exercise for durations in excess of 10 – 20 s.

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