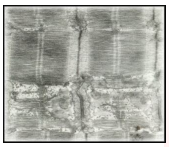
Catabolism in Skeletal Muscle
The Phosphagen System



- ***Overview of ATP Regeneration***
- ***Anaerobic vs Aerobic Metabolism***
- ***Creatine Kinase Reaction***
- ***Adenylate Kinase Reaction***
- ***Purine Nucleotide Cycle***
- ***Creatine Phosphate Shuttle***
- ***^{31}P MRS and Muscle Metabolism***

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ATP - *energy currency* of cell

Muscle contraction can increase the cellular demand for ATP 100-fold ! Resting [ATP] of 8 mmol/kg could be depleted in 2-3s of intense exercise!

The design and function of skeletal muscle metabolism is to meet this ATP demand as well as possible.

Skeletal muscle has sensitive biochemical controls of metabolic pathways involving the sudden activation and inhibition of specific enzymes.

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ATP Regeneration

Skeletal muscle can produce the ATP required to support muscle contraction from one or a combination of three metabolic reactions / pathways;

1. Phosphagen System - forming ATP from using creatine phosphate or two ADP molecules

2. Glycolysis - from blood glucose or muscle glycogen

3. Mitochondrial Respiration - the use of oxygen in the mitochondria

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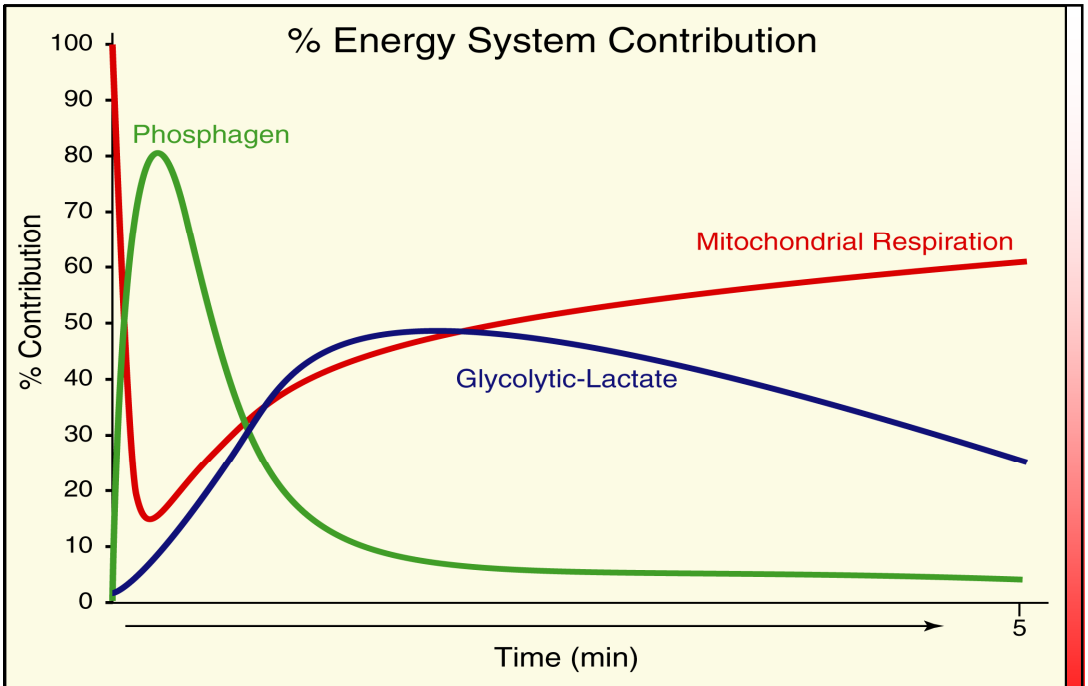

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Anaerobic vs Aerobic Metabolism... Old Terminology !

Anaerobic metabolism - does not require the presence of oxygen - creatine kinase & adenylate kinase reactions, and glycolysis.

Aerobic metabolism - the combined reactions of mitochondrial respiration - pyruvate oxidation, the TCA cycle, and the electron transport chain.

*These terms are **not entirely accurate** and it is inappropriate to differentiate the pathways as two extremes when they actually share a common central pathway (e.g., glycolysis) and occur simultaneously !*

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The Phosphagen System

The regeneration of ATP via the transfer of phosphate groups through either of two reactions:

1) Creatine Kinase Reaction (aka CrP reaction)
2) Adenylate Kinase Reaction

The creatine kinase reaction is the most immediate means to regenerate ATP. Why?

$$CrP + ADP + H^+ \xleftrightarrow{\text{creatine kinase}} ATP + Cr$$

Immediate changes in ADP and ATP concentrations!

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The Phosphagen System, cont'd

Note: The creatine kinase reaction is actually two separate reactions that are "coupled" together.

exergonic *"endergonic"*

$$CrP \longleftrightarrow Cr + Pi + ADP + H^+ + Pi \longleftrightarrow ATP$$

$$CrP + ADP + H^+ \xleftrightarrow{\text{creatine kinase}} ATP + Cr$$

Consumes H+ which helps delay acidosis!

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The Phosphagen System, cont'd

The ATP production capacity of the creatine kinase reaction relies on a store of CrP, ~ 26 mmol/kg wet wt. CrP content is slightly higher in fast twitch than in slow twitch muscle fibers.

Location of skeletal muscle creatine kinase:

- 4% on the outer mitochondrial membrane
  - essential for creatine phosphate shuttle
- 3% bound to myofibrillar proteins of sarcomere
- remainder free in cytosolic solution

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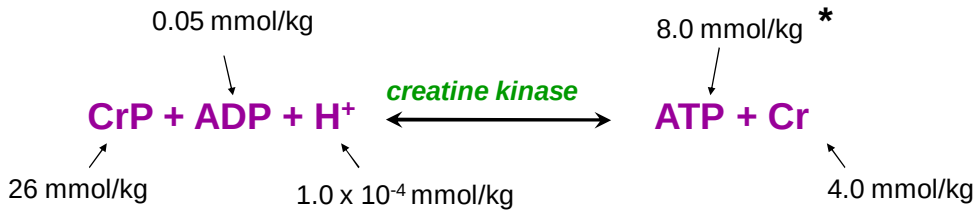
Increased Activity

At rest, the reaction is at equilibrium, therefore, the **ΔG ~ 0.**

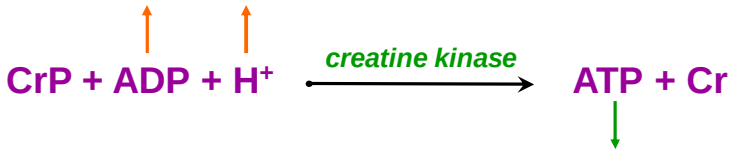


In other words, the substrate and product concentrations are approximately constant and therefore there is no net release of free energy.

** expressed mmol/kg wet wt in solution of cytoplasm*

Activity, cont.

During intense exercise, the reaction is pushed / pulled to the right, thereby breaking down CrP and forming ATP**.**
ΔG ~ -9.12



Initially, exercise results in an ↑ in substrate concentrations (ADP and H^+) and a ↓ in product concentrations (ATP).

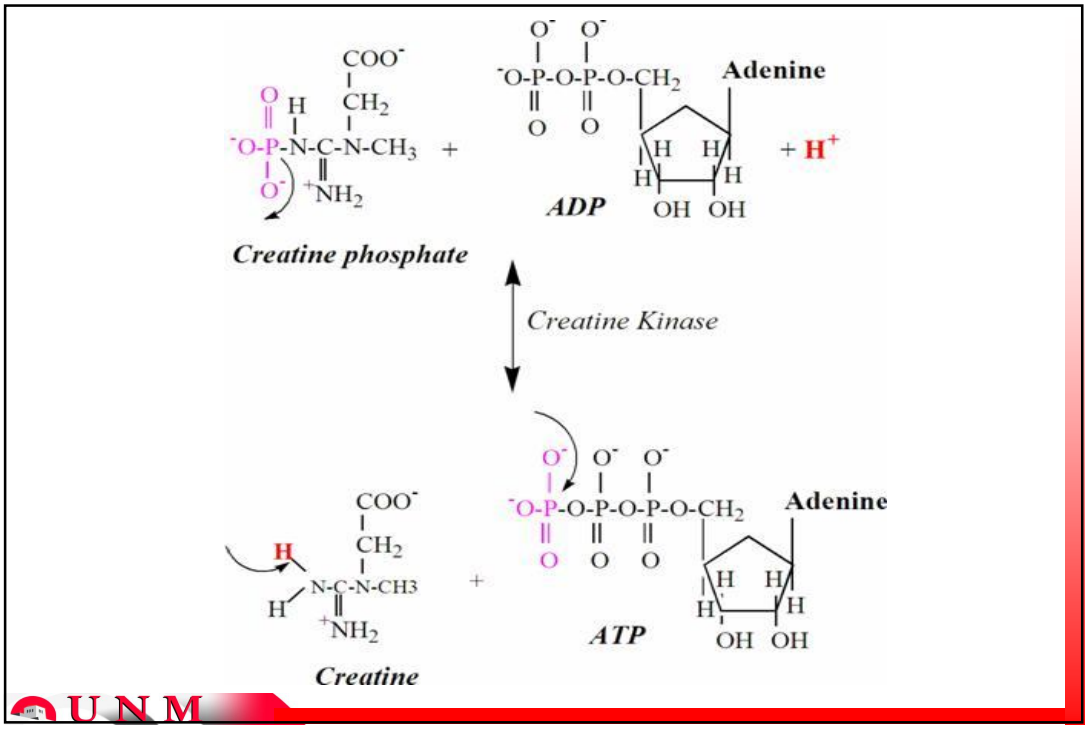


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TABLE 2.3

The concentrations of molecules that are important in energy metabolism within skeletal muscle at rest and after intense exercise to fatigue

MOLECULE	REST	FATIGUE
	(mmol/kg wet wt)*	
CrP	24.0	3.0
ATP	5.0	4.5
ADP	0.05	0.5
Cr	4.0	25.0
Pi	3.0	24.0
H^+	1.0×10^{-4}	4×10^{-3}
Lactate	1.0	25.0
Glycogen	200.0	75.0

Data are from references 3,4,6,7, and 11.
* These concentrations apply to molecules in solution in the cytoplasm of the cell. For a concentration unit applicable for precise bioenergetic calculations, the metabolites would be expressed relative to muscle water, which is estimated at approximately 78% of wet weight muscle, hence increasing the concentration shown by a factor of 1.3.

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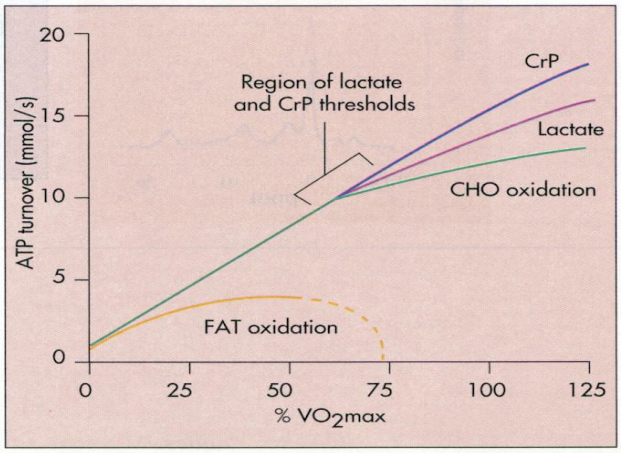
CrP also supplements ATP regeneration from mitochondrial respiration

Note the increased reliance on "anaerobic" sources of ATP regeneration as exercise intensity increases.

The changing metabolic conditions, and primary sources of ATP regeneration, during an incremental exercise test to VO_2max.



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The Phosphagen System, cont'd

The adenylate kinase reaction is similar to the creatine kinase reaction in that it is near equilibrium at rest.

ΔG=0

0.05 mmol/kg ↙ ↘ **ADP + ADP** ⟷ *adenylate kinase* **ATP + AMP** ↙ 5.0 mmol/kg

In other words, the substrate and product concentrations are approximately constant and therefore there is no net release of free energy.

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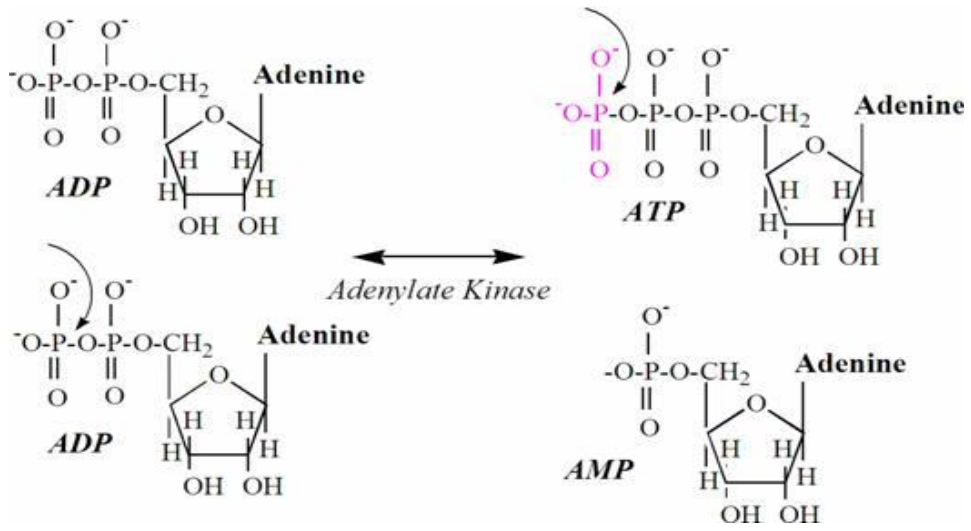
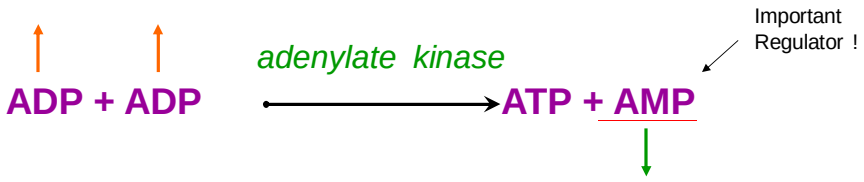


Changing activity

During intense exercise, the reaction is pushed/pulled to the right, thereby increasing the production of an allosteric activator (AMP).



Exercise results in an ↑ in substrate concentrations (ADP) and a ↓ in product concentrations (ATP).

Activity, cont'd.

Adenosine monophosphate (**AMP**) is the activator of the allosteric enzymes **phosphorylase** (glycogenolysis) and **phosphofructokinase** (glycolysis), thus stimulating increased carbohydrate catabolism and ATP regeneration.

However, continued increases in AMP would decrease the phosphorylation potential of the cell which is detrimental to the cell.

Phosphorylation Potential = [ATP] / ([ADP] [AMP] [ATP])

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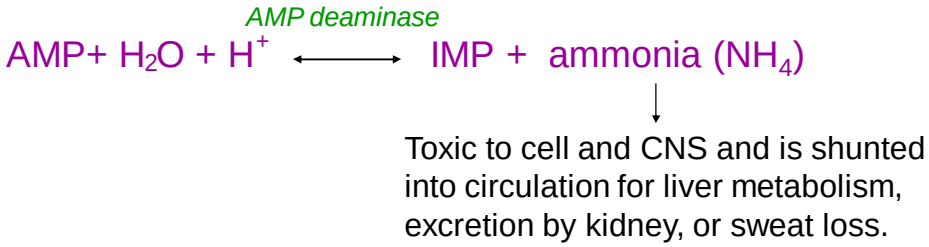
Purine Nucleotide Cycle

The conversion of AMP to IMP via the AMP deaminase catalyzed reaction.



The reaction is stimulated during acidic conditions (↑ H^+) and is reversed during recovery.

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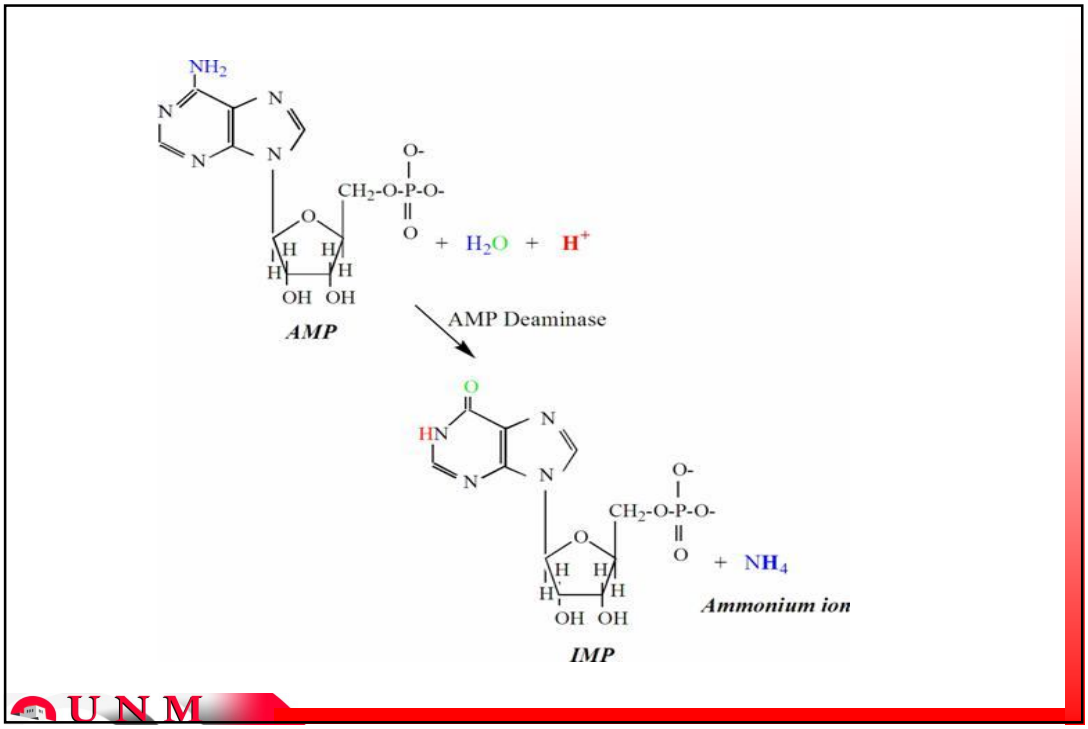
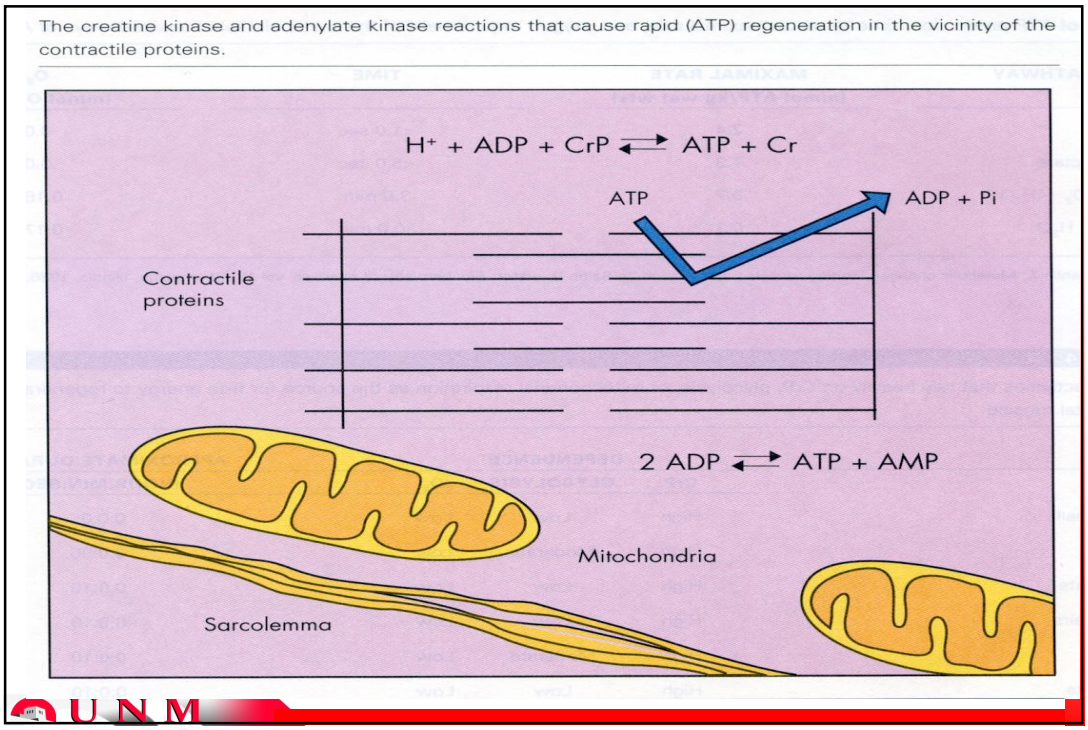
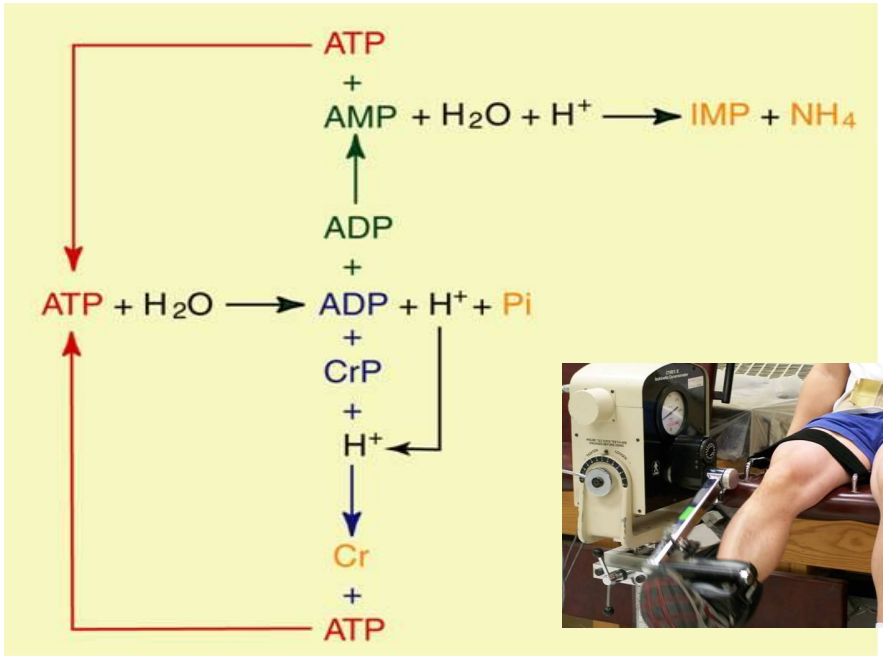

AMP
AMP Deaminase
IMP
Ammonium ion


The creatine kinase and adenylate kinase reactions that cause rapid (ATP) regeneration in the vicinity of the contractile proteins.
H+ + ADP + CrP ⇌ ATP + Cr
ATP
ADP + Pi
Contractile proteins
2 ADP ⇌ ATP + AMP
Mitochondria
Sarcolemma



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The phosphagen system can regenerate ATP at high rates

However, the finite store of CrP can be depleted in as little as 10 seconds.

Maximal rate of ATP production, time to reach maximal rate, and oxygen requirement of the metabolic reactions/pathways of ATP production

REACTION/PATHWAY	MAXIMAL RATE (mmol ATP/kg wet wts)	TIME	O_2 (mmol O_2/ATP)
CrP	2.4	<1.0 sec	0.0
Glucose ↔ Lactate	1.3	<5.0 sec	0.0
Glucose ↔ CO_2 + H_2O	0.7	3.0 min	0.167
FFA ↔ CO_2 + H_2O	0.3	30.0 min	0.177

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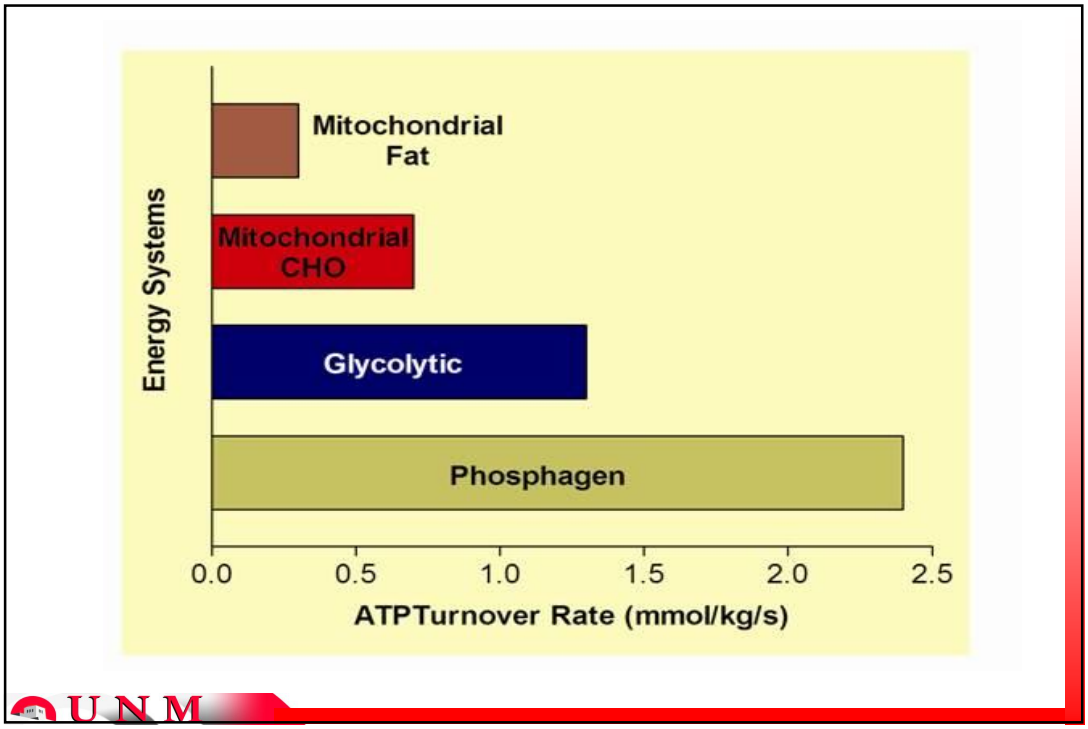


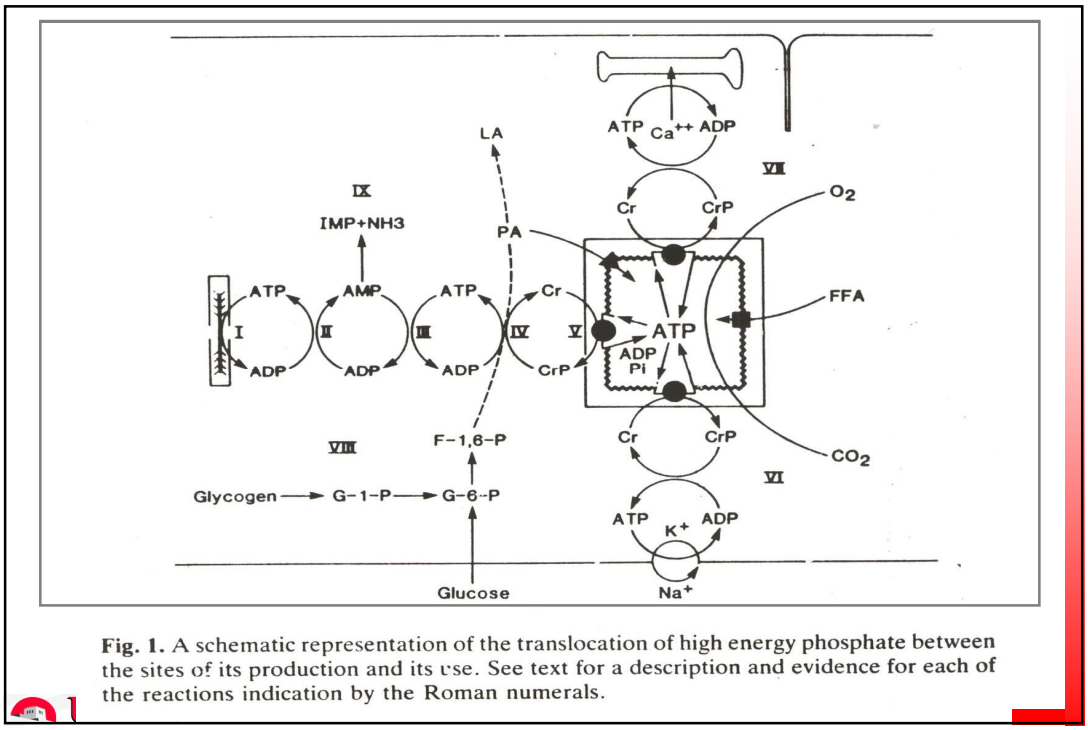
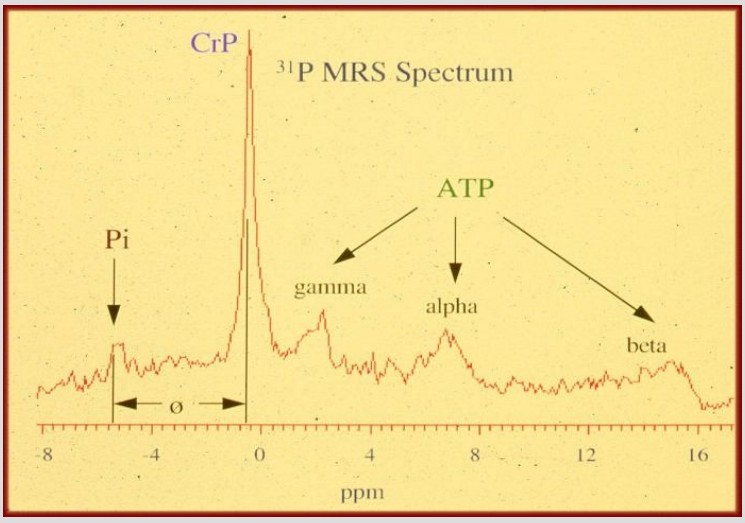


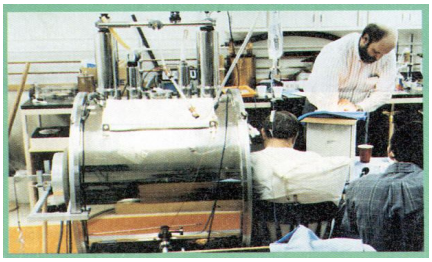
Fig. 1. A schematic representation of the translocation of high energy phosphate between the sites of its production and its use. See text for a description and evidence for each of the reactions indication by the Roman numerals.

Magnetic Resonance Imaging and Spectroscopy



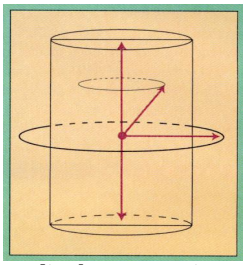
(^{31}P MRS)

1.



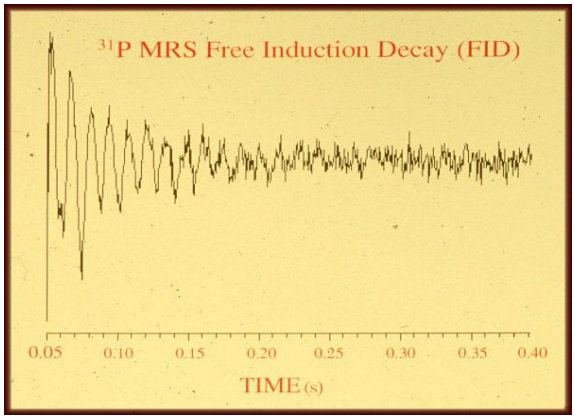
Magnetic field and high frequency radiofrequency energy input

2.



Rf energy displaces atomic electrons, causing energy to be released on their return to a normal axis

3.



Energy output from nuclei is acquired, and the frequency of the signal is specific to the atom of interest

TABLE 10.1

Properties of nuclei used in biologic magnetic resonance

NUCLEI	NATURAL ABUNDANCE	TISSUE* CONCENTRATION	SENSITIVITY†	MR TECHNIQUE	APPLICATION
Hydrogen (^{1}H)	99.9%	99	1.0	Imaging Spectroscopy	Metabolism Anatomy Fat distribution
Deuterium (^{2}H)	0.015%	Trace	0.001	Spectroscopy	Body water
Sodium (^{23}Na)	100%	0.08	0.093	Imaging	Anatomy
Phosphorus (^{31}P)	100%	0.075	0.066	Imaging Spectroscopy	Metabolism
Flourine (^{19}F)	100%	4×10^{-6}	0.083	Contrast imaging	Anatomy
Carbon (^{13}C)	1.1%	Trace	0.016	Contrast imaging Spectroscopy	Metabolism

Modified from American Hospital Association: *Hospital Technology Series* 4(3-4):1-235, 1985.
*Relative to total hydrogen = 100. †For the same number of nuclei at constant field strength.

magnetic resonance (MR)
the ability of objects to precess when forced out of alignment in a magnetic field

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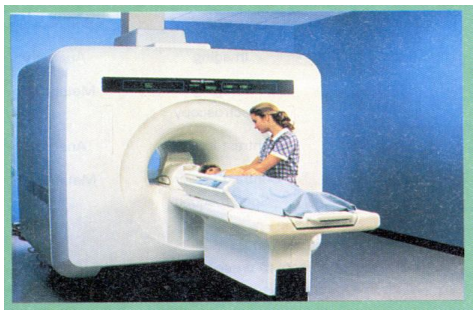
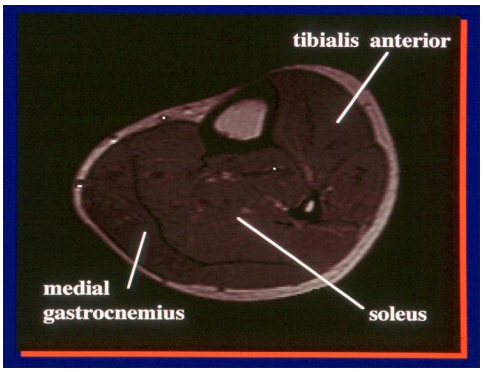


Whole body NMR Imager

Main medical applications of NMR is for non-invasive imaging of tissues within the body

A ^{1}H image of the lower leg

The higher the proton density, the brighter the image on an MR scan.



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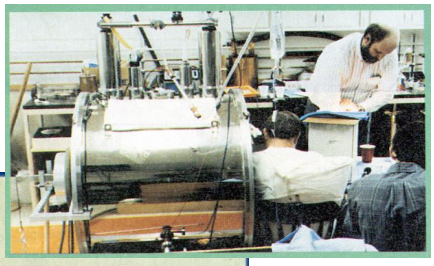
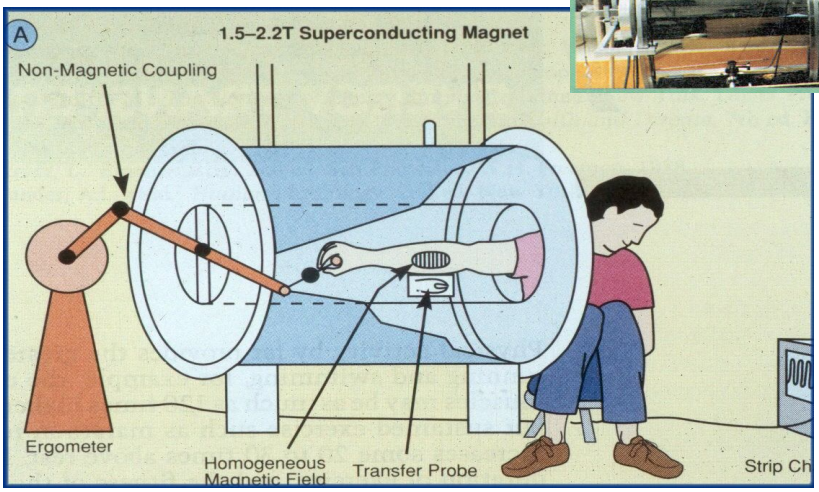
Spectroscopy

Magnetic field and high frequency radiofrequency energy input





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INTRACELLULAR pH:

Mean cell pH in the tissue volume scanned is calculated from the Pi vs PCr frequency difference:

$$pH = 6.75 + \log_{10}\left[\frac{(\delta - 3.35)}{(5.60 - \delta)}\right]$$

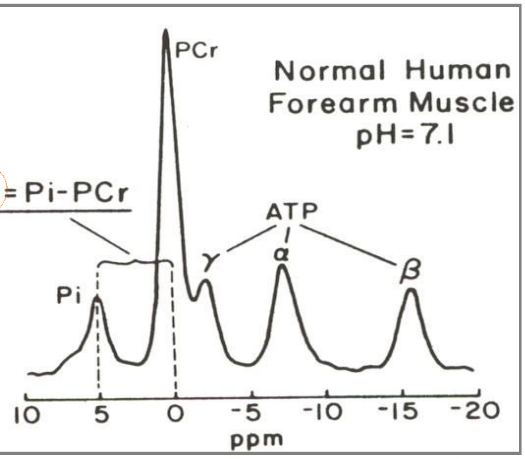

Figure 4—The measurement of intra-cellular muscle pH with ^{31}P NMR spectroscopy.

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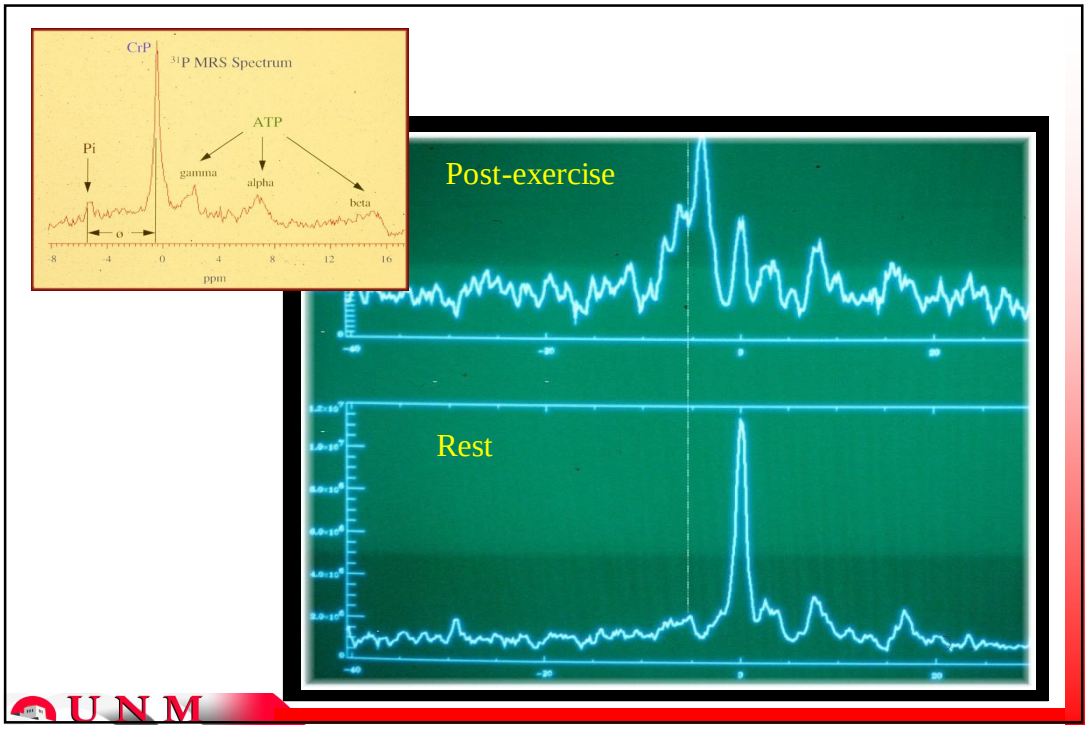
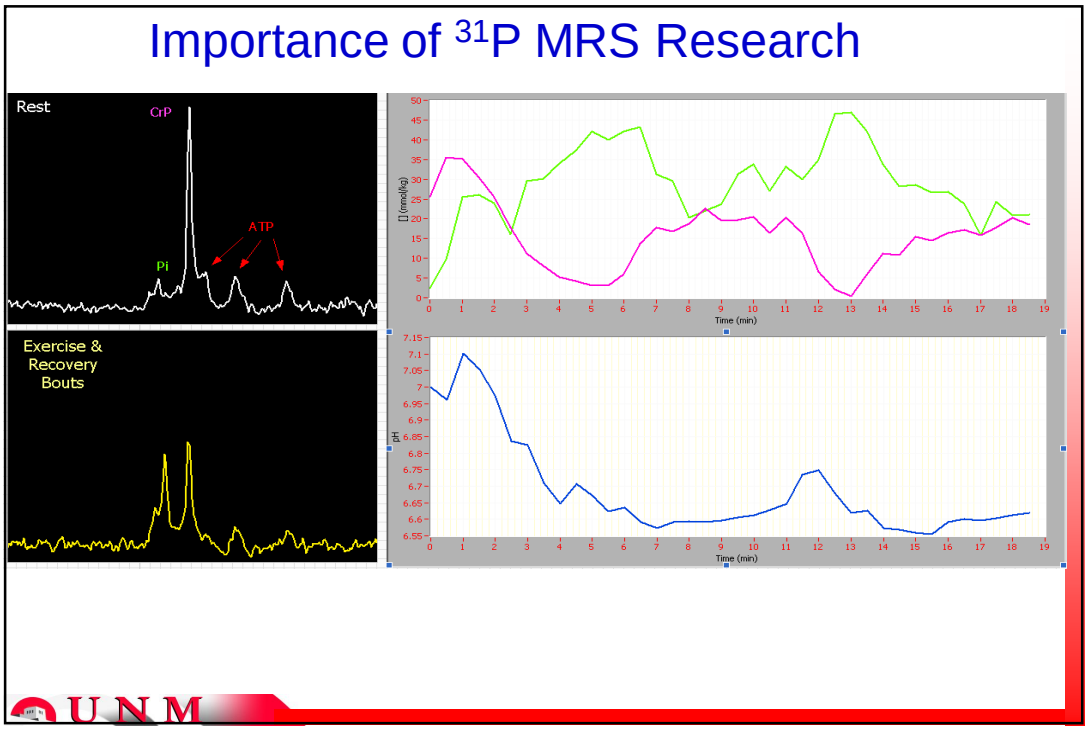
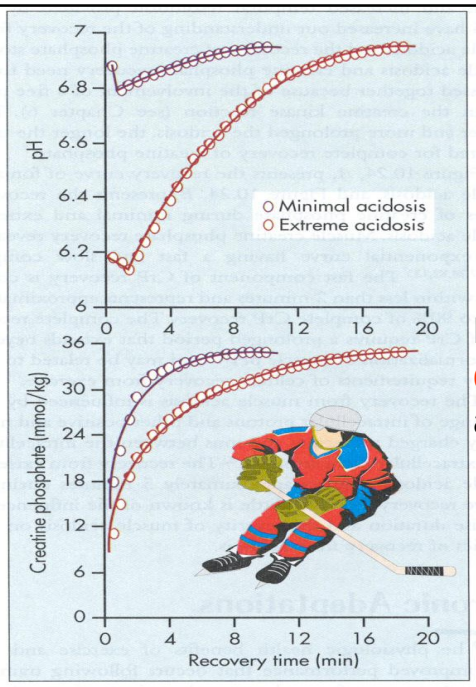

CrP
31P MRS Spectrum
ATP
Pi
gamma
alpha
beta
ppm
Post-exercise
Rest
UNM


Importance of 31P MRS Research
Rest
CrP
ATP
Pi
Exercise &
Recovery
Bouts
Time (min)
pH
Time (min)
UNM



Since the CrP reaction involves free protons, the greater the acidosis, the longer the recovery period.

Muscle CrP recovery reveals a dual exponential curve having a fast and slow component.

The fast component is complete within 2 min and represents ~ 80-90 % of complete CrP recovery.

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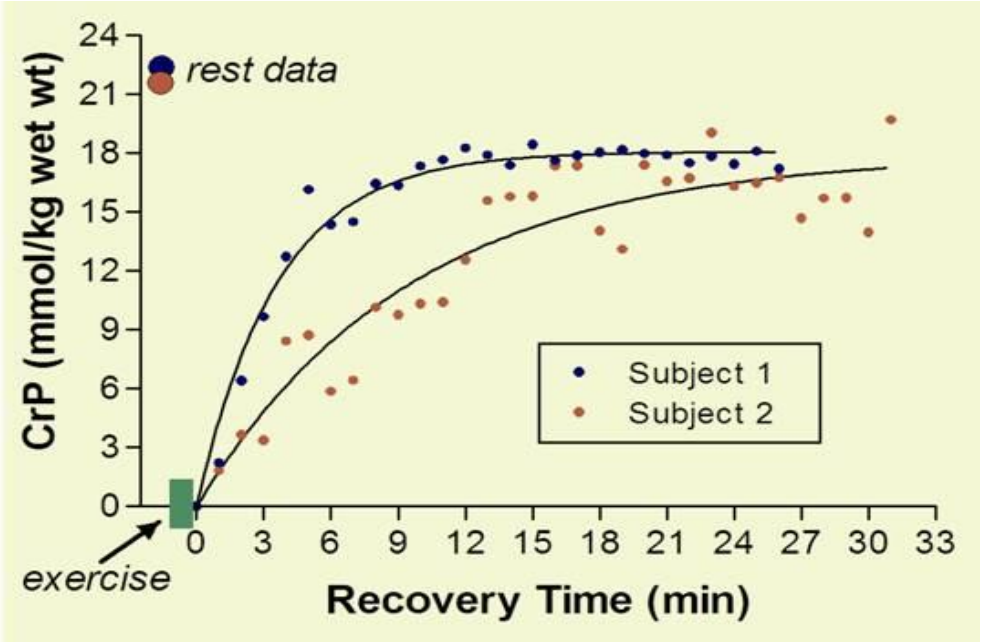

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