Targeting Antioxidants to Mitochondria

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Schedule of Topics

- Mitochondrial Structure & Function
- Triphenylphosphonium Targeting Strategy
- Clinical Correlation for Drug Design - Stroke
Mitochondrial Anatomy

http://www.life.uiuc.edu/crofts/bioph354/lect10.html
Membrane Translocation

Cytoplasm

Intermembrane Space

TOM
Membrane Translocation

Cytoplasm

Mitochondrial Matrix

TOM

TIM
Mitochondrial Matrix
Electron Transport Chain

NADH → Succinate → Q → III → IV

H^+ proton transport

O_2 + H_2O → H^+ → +

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ATP Synthase

http://www.life.uiuc.edu/crofts/bioph354/lect10.html
Sources of Free Radicals

NADH → Succinate

O_2 → H_2O
Sources of Free Radicals

- \( \text{MnSOD} \)
- \( \text{H}_2\text{O}_2 \)
- \( \text{Fe}^{2+} \)
- \( \cdot \text{OH} \)
- \( \text{ONOO}^- \)
- \( \text{NO} \)
- \( \text{O}_2^- \)
- \( \text{Aconitase Damage} \)
Initiation of Apoptosis

Intrinsic Pathway of Apoptosis

1. Cellular stress
2. Bax, Bid bind to outer mitochondrial membrane
3. Bak required to release mitochondrial factors
4. Cytochrome c released
5. Cyt c, ATP, Apaf-1 form complex
6. Caspase-9 & complex forms Apoptosome
7. Apoptosome activates Caspase-3

http://www.bioteach.ubc.ca/CellBiology/Apoptosis/
Extrinsic Pathway of Apoptosis

1. FasL binds to Fas
2. Receptors aggregate
3. Fas-Associated Death Domain (FADD) formed
4. Caspase-8 recruited
5. Death-Inducing Signal Complex (DISC) formed
6. Caspase-8 activated
7. Activated Caspase-8 activates Caspase-3
8. Caspase-3 initiates degradation of cell

http://www.bioteach.ubc.ca/CellBiology/Apoptosis/
Morphology of Apoptosis:

- Chromatin condensation
- Cell shrinkage
- Nuclear collapse
- Membrane blebbing
- Specific DNA Cleavage
- Cytoskeleton collapse
- Apoptotic bodies

http://www.bioteach.ubc.ca/CellBiology/Apoptosis/
Triphenylphosphonium Targeting

Triphenylphosphonium Targeting

\[ \Delta \Psi_m = 140-180 \text{ mV} \]

Intermembrane Space

\[ + \]  \hspace{1cm}  \rightarrow  \hspace{1cm} \text{Matrix}

Potential Energy

Triphenylphosphonium Targeting

\[ \Delta \psi = \frac{2.303 \, RT}{F} \log_{10} \left( \frac{[\text{cation}_{\text{in}}]}{[\text{cation}_{\text{out}}]} \right) \]

Under biological temperatures and conditions, there will be approximately a tenfold accumulation per \( \sim 60 \, \text{mV} \) increase in \( \Delta \psi \)

\( \Delta \psi_c = 60 \, \text{mV} \)

\( \Delta \psi_m = 140-180 \, \text{mV} \)

Triphenylphosphonium Targeting

MnSOD

O$_2^-$

Aconitase Damage

Lipid Oxidation

Neurological Stroke
Neurological Stroke

L-Arg

L-Cit

eNOS

NO•

NO•

NO•

NO•

NO•

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Neurological Stroke

Protection From Stroke
Neurological Stroke

L-Cit → NO• → Glutamate

iNOS

L-Arg

Proinflammatory Factors

L-Cit

NO• → nNOS

L-Arg
Neurological Stroke

**COX**

\[ 2O_2 + AA \rightarrow PGG + O_2^- \]

**Xanthine Oxidase**

\[ AMP \rightarrow Hypoxanthine \rightarrow O_2^- \]

**NADPH Oxidase**

Neutrophils \( \rightarrow O_2^- \)

**Mitochondria**

\[ O_2 + e^- \rightarrow O_2^- \]

(and \( •OH \))
Neurological Stroke

\[ \text{NO} + \text{O}_2^- \rightarrow \text{ONOOO}^- \]
Neurological Stroke

Morphology
- Infarction
- Inflammation and apoptosis

Biochemistry
- Ionic failure
- Anoxic depolarization
- Glucose use ↓
- Glutamate release
- Glucose use ↑
- Protein synthesis ↓
- Acidosis
- Oxygen extraction ↑
- Selective gene expression

Impairment of function ('penumbra')
- Minutes
- Hours
- Time
- Days and weeks

Structural lesion
Thanks For Your Attention!