Mar 29th, 8:30 AM - 9:50 AM

Evaluation of the Efficacy of Ubisol-Q10 Treatment in a Transgenic Mouse Model of Alzheimer's Disease

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ALZHEIMER'S DISEASE

Efficacy of Ubisol-Q10 Treatment in a Transgenic Mouse Model of Alzheimer’s Disease
WHAT IS ALZHEIMER’S DISEASE?

Most common neurodegenerative disorder worldwide, affecting 46.8 million individuals

https://cdn.evbuc.com/eventlogos/40265082/old.jpg
WHAT IS ALZHEIMER’S DISEASE?

- Most common form of dementia
- Characterized by the deterioration of neuronal synapses and widespread neuronal death in the brain\(^1\)
- This produces enlarged brain ventricles and cortical shrinkage

http://www.synsys.eu/general-public
WHAT IS ALZHEIMER’S DISEASE?

Two hallmarks of the disease:

1. Amyloid-β Peptide (Aβ) Plaques

2. Neurofibrillary Tangles containing Tau Protein

• Tau proteins, found abundantly in the CNS, stabilize axonal microtubules

• Tangles are thought to be due to imbalance between Aβ production and clearance

[Links]
https://www.alzheimer-forschung.de/alzheimer-krankheit/illustrationen_plaquesfibrillen.htm
http://healthland.time.com/2012/02/03/is-alzheimers-caused-by-contagious-proteins/
WHICH NEURONS & BRAIN REGIONS ARE INVOLVED?

• Cholinergic neurons specifically targeted.
• Specific region may be the nucleus basalis of Meynert – shown to deteriorate by more than 75%.
• Neuronal cell bodies in the basal forebrain.
• Innervate many areas of the cerebral cortex, thus cognitive functions such as memory are compromised.

https://psychiatricdrugs.com/neurology/acetylcholine/
https://neuroamer.wordpress.com/page/2/
AD SYMPTOMS

- Difficulty with simple tasks
- Language problems
- Difficulty with elaborate thoughts
- Disorientation
- Loss of reasoning capacity
- Memory loss
- Loss of initiative
- Lost objects
- Behavioural changes
- Emotional changes

http://www.doc-advice.com/alzheimers-disease/
CURRENT TREATMENTS

- No cure
- Symptomatic relief only

Drug treatments include:
- Cholinesterase inhibitors – ReminylER, Exelon, Aricept
- NMDA receptor antagonists – Ebixa (Memantine Hydrochloride)

Non-pharmaceutical treatments:
- Music therapy
- Pet therapy
- Aromatherapy & massage
- Natural health products

http://www.superama.com.mx
http://www.lundbeck.com/pt/produtos/neurologia/ebixa
http://www.founduseful.com/natural-health-products-online-and-over-the-phone/
http://www.indexmundi.com/canada/age_structure.html
Oxidative stress as a possible mechanism for neurodegeneration

**What is oxidative stress?**

- Some of the O₂ we breathe reacts to form free radicals → destabilize essential cell components
- Damage known as oxidative stress
- Young, healthy → strong compensatory/defense mechanisms to prevent oxidative damage
- Ageing weakens defenses such that ROS accumulate → apoptosis can be triggered
WHAT IS CoQ10?

- CoQ10, part of the ETC, sequesters electrons and stabilizes the mitochondria. This reduces the oxidative damage taking place. CoQ10 levels decline with age. 

[Diagram of the electron transport chain showing complexes I, II, III, and IV, with labels for NADH, FADH2, Q, Cyt c, Complexes I, II, III, IV, and O2.]

https://www.pinterest.com/pin/488951734528172000/
ARE ANTIOXIDANTS THE ANSWER?

- Antioxidants have been tested in the past

- **Oil-soluble formulation** of Coenzyme-Q10 was assessed – showed neuroprotection, but LOW bioavailability

- Very high effective doses: 400-1600 mg/kg/day

- For 70kg human → 112g/day

http://www.drblayney.com/Medical/
Our NRC collaborators synthesized a water-soluble formulation of CoQ10, known as Ubisol-Q10 which is much more bioavailable.

http://www.longevitylink.com/coenzyme-q10-supplement-facts-for-healthcare-professionals/
PREVIOUS WORK – PARKINSON’S DISEASE

Environmental Toxin PD Rat Model – therapeutic

![Graph showing TH+ Neurons % of Control for different groups.](image)

- Control (n=8)
- PQ2 (n=6)
- PQ1 (n=5)
- PQ2 + Ubisol-Q10 (n=7)

- Control: 100%
- PQ2: 17.6%
- PQ1: 41%
- PQ2 + Ubisol-Q10: 16%
Senescence: in response to stressors and damage, cells can adopt a permanent state of cell-cycle arrest.

PREVIOUS WORK – ALZHEIMER’S DISEASE

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A

- WS-CoQ_{10}  
+ WS-CoQ_{10}

10X  
40X

B

10X  
40X

---

% SA-β-galactosidase Positive

PTS  
WS-CoQ_{10}  
-  
-  
+  
+  
-  
#
PREVIOUS WORK – ALZHEIMER’S DISEASE

- **Autophagy**: a cellular stress response in which there is sequestration and breakdown of harmful or dysfunctional cellular components
  - Engulf damaged proteins/ organelles into autophagosome
  - Autophagosome fuses with lysosome → autolysosome
  - Degradation of cellular proteins
- **RT²PCR Array analysis** showing genes related to autophagy
SO WHAT NOW?

Can the Ubisol-Q10 formulation provide neuroprotection in an *in vivo* animal model?

TRANSGENIC MOUSE MODEL OF AD

- Transgenic mice, predisposed to develop early-onset AD, were obtained.
- Mice had two mutant human genes inserted:
  - Human amyloid-precursor protein (APP)
  - Human presenilin-1 (PS-1)

[Diagram of amyloid plaques and PS-1 complex]

PS-1 (γ-secretase complex) → APP → Aβ

http://www.nature.com/nature/journal/v425/n6958/fig_tab/425565a_F1.html
Obtained transgenic mice, predisposed to early-onset AD

Established control & experimental groups

Monitored mice for 14 months

Obtained blood samples & sacrificed mice to extract brains

Performed biochemical analyses & immunohistochemistry

**Experimental Design**

**Control** – regular drinking water

**Experimental** – Ubisol-Q10 supplemented water

• ELISA
• RT²PCR
IMMUNOHISTOCHEMISTRY – DECREASED AMYLOID-B PLAQUES IN BRAIN TISSUE

Control (Untreated)  Ubisol-Q_{10} Treatment  WT

Amyloid 50x Mag

Congo Red 50x Mag

500 um 1 mm
ELISA – DECREASED AMYLOID-B LEVEL IN SERUM

RT²PCR analyses still underway
FUTURE DIRECTIONS

• Understand if autophagy can be restored in the *in vivo* model through RT²PCR analysis

• Extend to other genetic models of AD → PS-2, APP¹⁰

• *Ultimately hope to develop Ubisol-Q10 as a treatment for those struggling with Alzheimer’s disease*
ACKNOWLEDGMENTS

• Dr. Siyaram Pandey & Krithika Muthukumaran
• Pandey & Cohen Labs
• Sponsors
REFERENCES


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