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

Annie S. Kanwar
University of Windsor, kanwara@uwindsor.ca

Follow this and additional works at: https://scholar.uwindsor.ca/uwilldiscover

This work is licensed under a Creative Commons Attribution-Noncommercial 4.0 License
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
Most common form of dementia

Characterized by the deterioration of neuronal synapses and widespread neuronal death in the brain

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

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?

Basal forebrain constellation of cholinergic neurons including basal nucleus of Meynert

1. Basal ganglia
2. Dorsolateral pontine tegmental constellation of cholinergic neurons

- Cingulate gyrus
- Neocortex
- Corpus callosum
- Thalamus
- Basal ganglia
- Amygdala
- Hypothalamus
- Hippocampus
- Pons
- Medulla
- Cerebellum

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

- Difficulty with simple tasks
- Language problems
- Disorientation
- Memory loss
- Lost objects
- Behavioural changes
- Emotional changes

- Difficulty with elaborate thoughts
- Loss of reasoning capacity
- Loss of initiative
- 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 $O_2$ we breathe reacts to form free radicals $\rightarrow$ destabilize essential cell components
- Damage known as oxidative stress
- Young, healthy $\rightarrow$ strong compensatory/defense mechanisms to prevent oxidative damage
- Ageing weakens defenses such that ROS accumulate $\rightarrow$ apoptosis can be triggered

http://www.kappit.com/tag/hydrogen-jokes/
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. 

The electron transport chain occurs in the inner membrane of the mitochondrion (membranes of cristae).

![Diagram of electron transport chain](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](image)
Senescence: in response to stressors and damage, cells can adopt a permanent state of cell-cycle arrest.

PREVIOUS WORK – ALZHEIMER’S DISEASE

[Graph showing percentage of SA-β-galactosidase positive cells with and without WS-CoQ10 and PTS treatment.]
**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)

PS-1 (γ-secretase complex) $\rightarrow$ APP $\rightarrow$ 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

**Control** – regular drinking water

**Experimental** – Ubisol-Q10 supplemented water

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

Control (Untreated)  
Ubisol-Q₁₀ Treatment  
WT

Amyloid  
50x Mag

Congo Red  
50x Mag
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


REFERENCES


