Mens Sana in Corpore Sano

The effect of metabolic factors and the actions of *Triiodo-L-thyronine* on mitochondrial morphology

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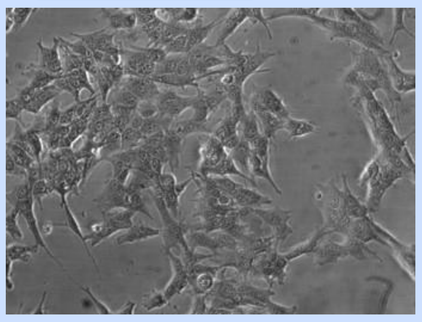
Background

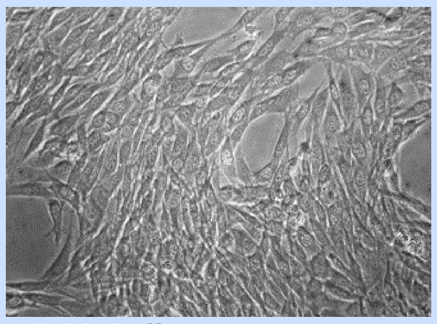
- Epidemiological studies have highlighted that **lifestyle and metabolic factors** can drive the risk of developing neurodegenerative diseases such as Alzheimer's disease (AD) and other dementias (Popa-Wagner et al., 2020; Muddapu et al., 2020).
- Well-known unhealthy lifestyle choices **change the levels of blood metabolites** that have adverse effects on our physiology (Beuchel et al., 2019).
- AD is characterised by **mitochondrial dysfunction and oxidative damage**. Aberrant levels of metabolic factors, such as homocysteine (Hcy), copper and amyloid-β (Aβ), can damage neurons, which set the scene for the progression to dementia.
- ***Triiodo-L-thyronine*** (T3) is an active form of thyroid hormone that has been demonstrated to be a **central regulator of mitochondrial activity**, with reduced T3 levels being associated with **cognitive decline** in AD.
- A depletion of T3 receptors is present in AD brains, specifically in the hippocampus, an area primarily affected by AD (Sutherland et al., 1992).

Methods



SH-SY5Y Cells
(human neuroblastoma cells)

Treated with 100uM of homocysteine- stressor

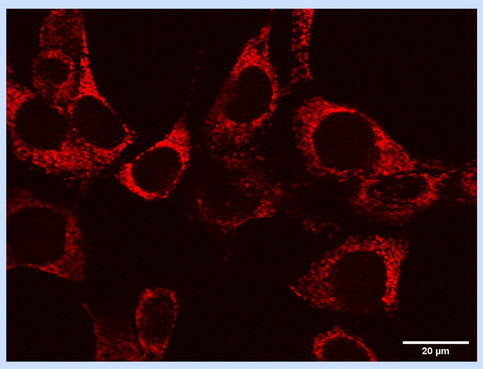


HT-22 Cells
(murine hippocampal neuronal cells)

Treated with 10uM of copper chloride - stressor

Treated with 10uM of Aβ 1–42 peptide

Labelling mitochondria with MitoRed to explore the morphology



Cells were either…

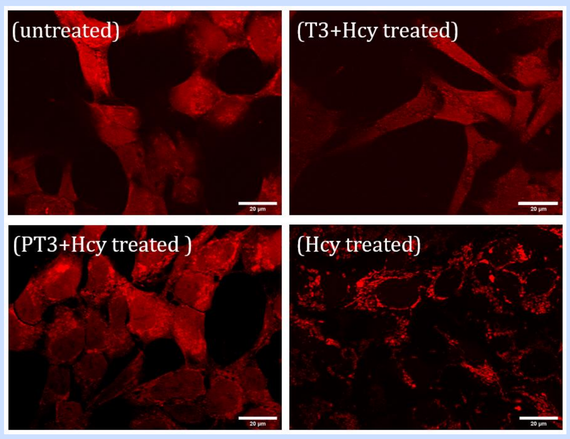
a) Pre-treated with T3 24 hours before administering the stress condition for 24 hours (**PT3**)
b) Treated with T3 alongside the stress condition for 24 hours (**T3**)

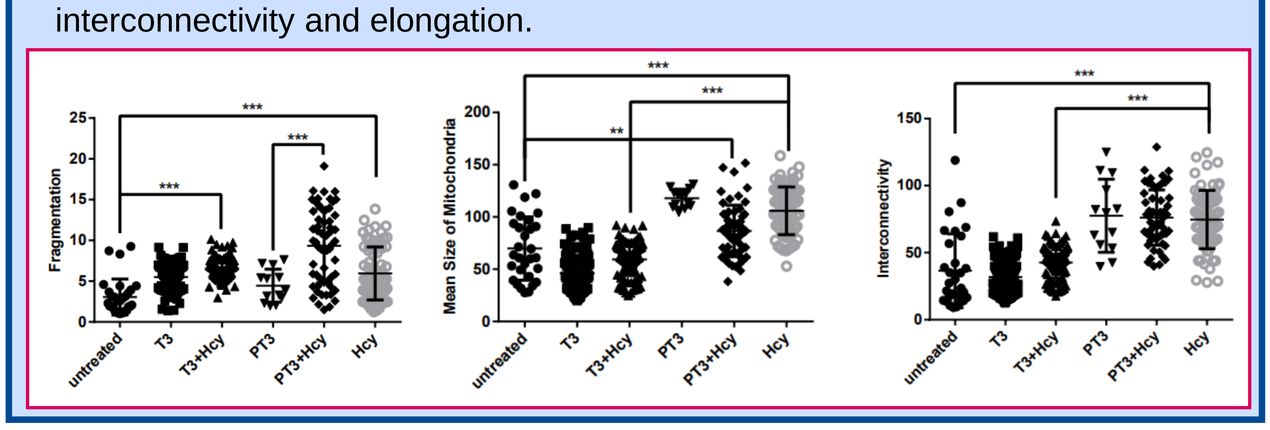
Qualitative Changes examined in mitochondrial morphology:

Mean number → Mean size → Fragmentation → Interconnectivity → Elongation

Results- Hcy treated SH-SY5Y Cells

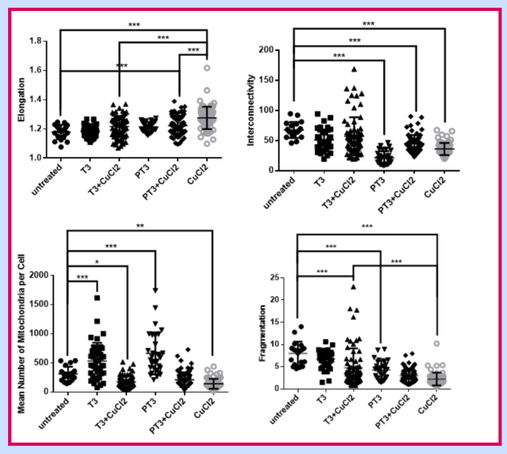
- Hcy treatments lead to significant alterations in all areas of mitochondrial morphology explored.
- Cells pre-treated with T3 had more significant fragmentation than homocysteine.
- T3 had a modulating effect on mitochondria count, size, interconnectivity and elongation, sustaining typical levels.
- Prolonged exposure to T3 caused further damage to the mitochondrial size, fragmentation, interconnectivity and elongation.

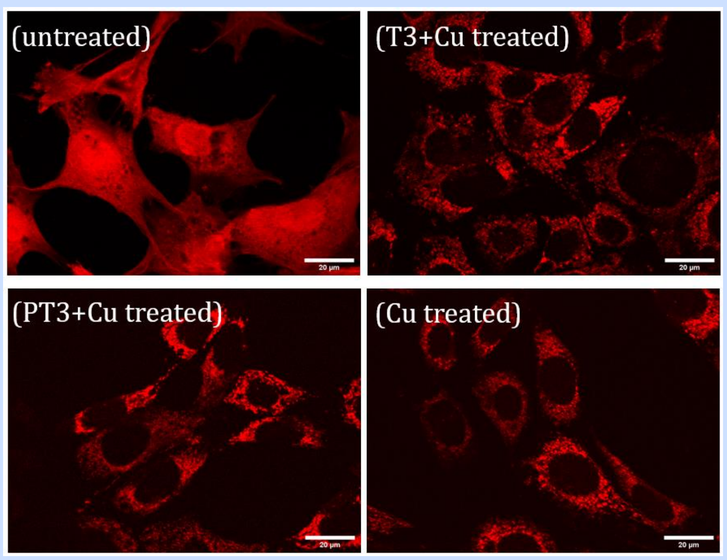




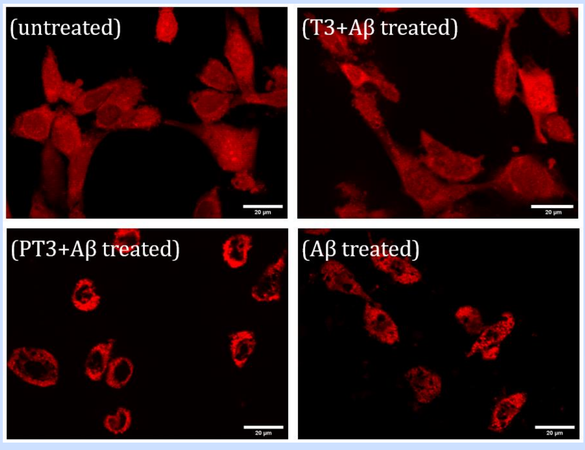
Results- Copper treated HT-22 Cells

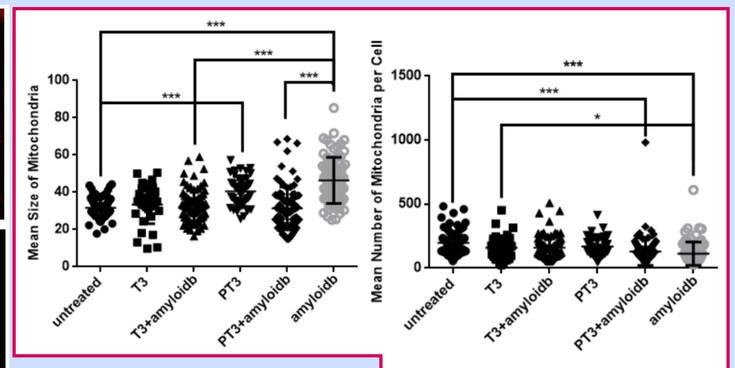
- Copper exposure lead to alterations in mitochondrial count, fragmentation, interconnectivity and elongation.
- Longer exposures to T3 did not damage mitochondrial morphology.
- T3 had a rescuing effect on mitochondrial count, fragmentation and recovery.
- Following copper treatment, mitochondrial interconnectivity sustained normal levels, however exposure to T3 decreased the interconnectivity, suggesting toxicity.

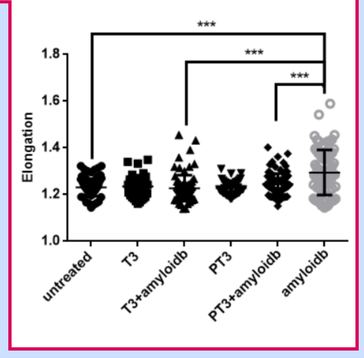




Results- Amyloid-β treated HT-22 Cells







- Aβ significantly decreased mitochondrial number and fragmentation but significantly increased size and elongation. It had no significant effect on mitochondrial interconnectivity.
- T3 had a rescuing effect on mitochondrial size and elongation, suggesting that it supports mitochondrial growth.
- Prolonged T3 exposure further damaged the mitochondrial size.

Conclusions and Research Implications

- Metabolites alter and damage mitochondrial morphology.
- T3 influenced mitochondrial activity by **modulating and sustaining** typical mitochondrial morphology, highlighting the protective role of thyroid hormone in regulating mitochondrial dynamics.
- The **prolonged T3 treatment destroyed the mitochondria**, mimicking the stressor conditions.

- As longer exposures to T3 have detrimental effects on the mitochondria, it may **not be safe to use long-term**.
- **Hyperthyroidism-like problems** appear to be present in the three metabolite conditions. This condition inflicts structural and functional damage to mitochondria, eventually leading to energy depletion and cardiac dysfunction, which is significantly associated with increased risk of AD (Maity et al., 2013; Qiu et al., 2006).
- This highlights that more **targeted approaches to the precise lifestyle modifications** that can be made to reduce the probability of developing dementia and improve brain health are needed.

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