Webinar Q&A Report:
Strategic Approaches to Age-Related Metabolic Insufficiency and Transition into Dementia Syndrome

1. **Can regular exercise, if started early in life, alleviate the occurrence of dementia?**

   This is not clear since there are no studies yet, but exercise is a risk factor for osteoporosis, for example.

2. **Could you elaborate on how isoflurane is neuroprotective with examples, mechanism, etc.?**

   There are multiple papers on comparing anesthetics for neuroprotection - see Kudo C 2008 + 2013 for example.

3. **Can you discuss how limitations in oxygen supply and mitochondrial function could impact the ability to utilize alternate fuel sources like ketones and lactate?**

   Oxidative phosphorylation with both ketones and lactate still requires oxygen (O_2) supply (like glucose) but this is rarely limited since they can diffuse easily across the Blood Brain Barrier (BBB). Main difference is monocarboxylate transporters (MCT) versus glucose transporters (GLUTs).

4. **How does sleeping influence aging and dementia? How does not adjusting to the circadian rhythms influence this?**

   Sleeping can influence both circadian rhythms as well as glymphatic flow and brain clearance - see Nedergaard M on both issues.

5. **Does caloric restriction improve the ability of aged animals to switch from glycolysis to oxidative metabolism?**

   Caloric restriction provides more ketones and still requires oxidative metabolism like glucose but through alternative routes in mitochondria.

6. **Your Alzheimer's Disease (AD) mouse model has APP mutation, but not Tau protein mutation. You also observed Tau tangles in your model. Do you know when the Tau tangles start to appear in your model?**

   Yes, around 24 weeks - see Colton CA et al, 2014 + 2015 for more detail.

7. **Is there a predominance of mitochondrial factors over vascular factors to explain metabolic insufficiency?**

   Many factors are involved - changes in incoming supply with vascular pathology, lack of vascular reactivity for neurovascular coupling, lack of Glut-1 transporters, and enhanced glucose needs with aging.

8. **Does hyperglycemia in Type 1 diabetes mellitus (T1DM) patients lead to dementia?**

   When DM is out of control, then there is high risk of small vessel disease and other vascular pathology, but it's not clear if this is directly hyperglycemia or an inability of cells to use the glucose.

9. **Can we reversibly reduce the neurons energy demand in a short period to treat the metabolic insufficiency?**

   Possible, then but then brain function would be perturbed - reduced cognition, memory, etc.

10. **Can exogenous ketones work as brain energy substrate in the absence of fasting in dementia?**

    Yes, and are an excellent source of energy for oxidative phosphorylation.

11. **What is the difference between caloric restriction and intermittent fasting? Which one is better for delaying aging or dementia? And if we compare to keto diet?**

    See Mattson M 2019 - the relative level of ketones versus glucose is the important factor, possible through many routes.

12. **Just curious, which is better source of fuel for long term brain health: glucose or fat, or a combination perhaps?**

    Not clear - caloric restriction (ie, every other day diet - Mattson M 2019) clearly leads to more ketones and leads to enhanced longevity in every animal model studied (except humans).

13. **Are there insulin receptors on neurons or astrocytes that regulate metabolism or is metabolic activity independent of insulin?**

    Glucose entry into neurons and astrocytes is via GLUT transporters (3 and 1, respectively) and insulin is not needed for glucose entry. However, insulin and IGF-1 are both important growth factors.

14. **Empaglifozin (Jardiance) affects glucose transporters and is taken for diabetes, etc. What is the effect of empaglifozin on the glucose transport, etc. in the human brain, especially in respect to the aging brain?**

    GLP-1 agonists are currently being tested to enhance glucose transport into the brain in Alzheimer's disease.

15. **Hot flushes include changes in brain blood flow. Is this a "stress" in the context of your work?**

    No - a stress would be where neurons want more substrate (via enhanced blood flow) and it is not available due to restrictions (ie, supply-demand mismatch).

16. **Estrogen/estrogen receptor activation regulates pericyte processes/BBB. How do you see estrogen action in your stress and aging in women?**

    Most ongoing studies of aging include both pre-menopausal and post-menopausal mice, for example as well as both genders.

17. **Since both male and female brains produce estrogen, should aging persons augment their estrogen as the gonads fail?**

    Hormone replacement therapy (HRT) remains highly controversial in post-menopausal women due to high risks and side effects, so there's currently no clear answer.

18. **Are there and what is the distribution of GLUT-2 receptors? Could this be related to the neuroprotective effect of high glucose levels in vitro?**

    GLUT-2 is mainly located in the liver, pancreas, intestine, and kidney rather than brain: GLUT-1 is the main BBB and astrocyte transporter for glucose, while GLUT-3 is for neurons.

19. **Is sleep a high energy demand process or the opposite?**

    Different phases of sleep variably show decreased neuronal activity (slow wave sleep) whereas REM sleep activated neurons are similar to awake state - we need both phases of sleep.

20. **Does vascular leakage affect brain metabolic function?**

    Not certain but is typically associated with vessel pathology, increased edema, and often hemorrhages into the brain, so is considered pathological in nature.

21. **Are medium chain triglycerides a good alternative energy substrate like ketones in dementia and aging? If yes, would they also be more beneficial when combined with lower glucose?**

    The brain does not use triglycerides directly, but the liver (and fat cells) can convert these into ketone bodies useful for the brain - acetoacetate and beta-hydroxybutyrate.

Contact Details

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