PERSPECTIVES

Can the Energetic Profile of Skeletal Muscle Predict Risk of Cognitive Impairment?

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A Perspective on "Mild Cognitive Impairment and Donepezil Impact Mitochondrial Respiratory Capacity in Skeletal Muscle"

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders that affects memory, thinking, and behavior, as humans age. AD is a complex, multifactorial condition that lacks many treatment options from a clinical perspective. Further complicating treatment of AD is the presence of other secondary issues such as peripheral insulin resistance, low physical activity, high blood pressure, obesity, and so on. Thus, clinicians are tasked with diagnosing patients without proven basic scientific analytical tools while the patient is presenting with other clinical issues.

Morris et al. sought to assess mitochondrial capacity in skeletal muscle of patients with early stages of cognitive decline and determine if respiratory function was associated with genetic risk (Apolipoprotein ε4; *APOE4*) or non-genetic risk factors (overweight/obesity, physical activity, and so on).[1] Mitochondrial respiratory capacity was assessed in fiber bundles from skeletal muscle biopsies from patients with mild-cognitive impairment (MCI, ($n = 11$)) or MCI patients treated with donepezil (MCI + med, ($n = 15$)) or cognitive healthy age-matched patients (CH, $n = 24$). Donepezil is a cholinesterase inhibitor that appears to improve memory and awareness and is prescribed to patients suffering from dementia. The data demonstrate that MCI patients had lower palmitoylcarnitine ADP-stimulated respiration (State 3) values compared to the CH or MCI + med groups, which was associated with poor coupling control and leak ratios in the MCI group. Interestingly, the same results were not seen when the substrate was changed to pyruvate, suggesting unique nuances exist within the mitochondria of skeletal muscle from MCI patients. In follow up experiments, RNA sequencing analysis of the biopsies from each subject identified that genes associated with energetic regulation were downregulated in the MCI group compared to the other groups, thus confirming the biochemical results. Interestingly, the donepezil treated MCI subjects compared to untreated counterparts (MCI + Med versus MCI) elucidated a substantial drug-effect (~692 differentially expressed genes) on muscle gene expression suggesting an effect of cholinesterase inhibitor directly on the skeletal muscle. This is consistent with other small molecules that are proposed to have therapeutic effects on AD, where the molecules appear to preferentially accumulate in skeletal muscle.[2]

Often discussed during AD is the accumulation of amyloid and phosphorylated tau in the brain and neuronal tissue, however, what is often overlooked is amyloid buildup is not specific to the brain and occurs in various peripheral tissues including skeletal muscle. The increase in amyloid has been documented in preclinical models of AD and in AD patients,[3,4] however, the effect of amyloid accumulation in skeletal muscle needs further investigation. Skeletal muscle appears to accumulate amyloid as part of the aging process,[5] which may be exacerbated with the onset of AD, and potentially resulting in inclusion body myositis.[6] Accumulation of amyloid has been associated with reduced neuronal innervation of skeletal muscle,[7] alterations in mitochondria membrane potential and content,[5] and lower maximal respiratory capacity of skeletal muscle compared to control.[3] Acute delivery of full-length amyloid precursor protein to skeletal muscle was sufficient to alter mitochondrial respiratory kinetics suggesting that amyloid effects on muscle occur rapidly and may be detectable in early phases of AD.[3] Collectively, the data indicate that the skeletal muscle is affected during MCI, a precursor to AD, suggesting an intriguing possibility that assessment of skeletal muscle may provide an avenue to uncover a measurable biomarker for AD diagnosis or determining susceptibility to other forms of dementia.

MCI is the earliest clinical stage of AD, and represents a possible window for therapeutic intervention that could prevent or attenuate further symptom development.[1] Unfortunately, identification of AD in the earliest stages remains a challenge, thus making timing of an intervention more difficult. Thus, if patients with MCI or AD have a unique bioenergetic signature in their skeletal muscle tissue, it might be possible to use that as a biomarker for early identification of patients providing an improved window for therapeutic intervention. Until now, any attempts to understand energetics in skeletal muscle of AD patients had been primarily been conducted in preclinical models, but Morris et al. have now provided important data demonstrating similar results in humans. Further, the data indicate that the bioenergetic signature may be more specific than just a loss in capacity due to the different substrate response. It will be important to further evaluate the energetic signature of the mitochondria in skeletal muscle, using innovative mitochondrial measures that is[8] in MCI or AD patients to determine if the readout is unique enough to have diagnostic possibility for clinicians. Thus, if a signature is identified that can be assessed non-invasively, as pointed out by the authors, performing longitudinal studies will provide more clear understanding of when the onset of skeletal muscle changes may occur in the relation to changes in cognitive function, since the real value will lie in the possibility that energetic changes in skeletal muscle may precede changes in cognitive function. Overall, this contribution is incredibly important to the field, as it hopefully will encourage an innovative scientific movement toward early diagnosis and development of reliable biomarkers that improve the possibility of intervention .[1] In conclusion, the study by Morris et al. was difficult in scope, but with the application of rigorous methods and a well-designed approach, the authors have provided the field critical data that will provide a meaningful road map moving forward towards developing approaches for patients that are at risk for developing MCI or AD.[1]

Conflict of interest statement

The author has no conflicts of interest to declare.

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