CD38 dictates age-related NAD$^+$ decline and mitochondrial dysfunction: perspectives on its role in brain energy metabolism

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Introduction : Nicotinamide Adenine Dinucleotide (NAD) levels decrease during aging, and are involved in age-related metabolic decline. To date, the mechanism responsible for this reduction in NAD has not been elucidated. One of the hallmarks of aging is the cognitive impairment, that contributes to frailty of olders and compresses the period of decline in fitness with the increase in healthspan, leading to a state that olders depends on relatives to pursue basic daily tasks. Up to date, the mechanisms involved in brain energy metabolism towards cognitive impairment are poorly understood.**Objectives:** Our main goal is to investigate the participation of NAD metabolism in processes that regulates energy metabolism in aging and brain metabolism that could related to cognitive impairment.**Materials and Methods:** We addressed our goals using techiniques as western blot, mitochondrial function by high resolution respirometry, enzyme activity by fluorimetric and spectrometry measurements and measurements of pre pulse inhibition to asses brain network states. We performed these studies in brain mitochondria isolated from CD38KO mice, known to have higher levels of NAD, compared to wild-type animals. **Discussion and Results:** We demonstrate that expression and activity of the NADase CD38 increase with aging, and that CD38 is required for the age-related NAD decline and mitochondrial dysfunction via a pathway mediated at least in part by regulation of SIRT3 activity. We detected that brain mitochondria of CD38KO mice, demonstrates a significantly increase in energy metabolism enzymes and also antioxidant enzymes activities, as mitochondrial hexokinase and thioredoxine reductase compared to wild-type animals. **Conclusion:** In conclusion, we detected that CD38 is the main enzyme responsible for degrading NAD in aging and controls age related mitochondrial dysfunction. Also, CD38 can participate in processes that maintains brain energy metabolism.More studies have to be done to demonstrate the effect of these findings in brain function decline, but we believe that these results could show a perspective in protection against brain metabolism dysfunction with NAD replacement therapy.

Key words: CD38, NAD$^+$, mitochondrial function, aging, brain energy metabolism