Impact of sex and high-fat diet on brain energy metabolism dysfunctions associated with the development of Alzheimer's Disease neuropathology

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Biliverdin reductase-A (BVR-A) is a pleiotropic enzyme involved in several intracellular processes.A key role for BVR-A was proposed for the regulation of the insulin signalling (IS) and studies from our lab showed that loss of BVR-A leads to insulin resistance both in peripheral tissues and in the brain.Here, we tested the hypothesis that reduced BVR-A protein levels represent an early event in the sequela of the molecular events leading to brain insulin resistance.We evaluated whether loss of BVR-A prompts an increase of mitochondrial stress in response to insulin, thus resulting in brain dysmetabolism and neurodegeneration.We fed C57BL/6J mice with a chow diet (CD) or a high fat diet (HFD) – known to promote brain insulin resistance – for 1, 3 and 8 weeks.Peripheral metabolic measurements and cognitive tests were performed. In addition, IS activation and oxidative stress markers levels in the hippocampus were evaluated. To confirm the role of BVR-A, similar analyses plus the evaluation of mitochondrial function, were performed in the hippocampus of BVR-A KO mice.Our results show that HFD induced peripheral metabolic alterations and cognitive dysfunctions at each time points.1 week of diet is enough to promote a reduction of BVR-A levels in the brain, that is associated with the dysfunction of IS and an increase of oxidative stress markers levels. Such alterations occur in both sex although they are more prominent in female mice fed with HFD. Similar alterations were observed in BVR-A KO mice along with an impairment of mitochondrial function characterized by reduced OCR and the activation of UPRmt, that were further aggravated following the HFD.These data suggest that the loss of BVR-A triggers the impairment of the IS in the brain, and that such alterations are more severe in females. Moreover, the loss of BVR-A leads to mitochondrial impairment and brain dysmetabolism, which likely contribute to accelerate the development of AD neuropathology.