Palmitic acid reduces the autophagic flux in hypothalamic neurons by impairing autophagosome-lysosome fusion and endolysosomal dynamics

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Abstract

High-fat diet (HFD)-induced obesity is associated with increased cancer risk. Long-term feeding with HFD increases the concentration of the saturated fatty acid palmitic acid (PA) in the hypothalamus. We previously showed that, in hypothalamic neuronal cells, exposure to PA inhibits the autophagic flux, which is the whole autophagic process from the synthesis of the autophagosomes, up to their lysosomal fusion and degradation. However, the mechanism by which PA impairs autophagy in hypothalamic neurons remains unknown. Here, we show that PA-mediated reduction of the autophagic flux is not caused by lysosomal dysfunction, as PA treatment does not impair lysosomal pH or the activity of cathepsin B.Instead, PA dysregulates autophagy by reducing autophagosome-lysosome fusion, which correlates with the swelling of endolysosomal compartments that show areduction in their dynamics. Finally, because lysosomes undergo constant dynamic regulation by the small Rab7 GTPase, we investigated the effect of PA treatment on its activity. Interestingly, we found PA treatment altered the activity of Rab7. Altogether, these results unveil the cellular process by which PA exposure impairs the autophagic flux. As impaired autophagy in hypothalamic neurons promotes obesity, and balanced autophagy is required to inhibit malignant transformation, this could affect tumor initiation, progression, and/or response to therapy of obesity-related cancers.

Keywords

Author Keywords: Palmitic acid; high-fat diet; lysosomes; central nervous system; hypothalamic neuronal cells; autophagy; electron microscopy; Rab7; obesity-associated cancers
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