

INSULIN RECEPTOR SUBSTRATE- 2 (IRS-2) DOSE- DEPENDENT REGULATION OF ENERGY HOMEOSTASIS IN THE BRAIN

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Central regulation of appetite or calorie restriction extends life span and improve metabolic syndromes such diabetes and obesity. In *Drosophila melanogaster*, partial inhibition of Insulin/IGF-1 signaling pathways—especially loss of *chico*, Insulin Receptor Substrate (IRS) increases adiposity, reduces fertility, and extends the life span. Similar phenotypes are seen in mice lacking IRS2. To investigate how IRS2 signaling coordinates central nutrient homeostasis, we studied signaling and neuropeptide response in young (8 wks) and old (8 months~) systemic *Irs2^{+/-}* and *Irs2^{-/-}* mice, or in mice only lacking *Irs2* in the brain—*Blrs2^{+/-}* or *Blrs2^{-/-}* mice. Interestingly, food intake decreased in old *Irs2^{+/-}* and *Blrs2^{+/-}* mice compared to old wild-type mice, however, old *Blrs2^{-/-}* mice displayed an increased appetite and developed obesity. In order to examine neuropeptides expression involved in feeding behavior, we measured by RT-PCR AgRP, NPY, and POMC mRNA levels in the hypothalamus of young and old mice. During fasting, the expression of each neuropeptide decreased in old *Irs2^{+/-}* and *Blrs2^{+/-}* mice. Upon refeeding, the expression of orexigenic neuropeptides decreased and POMC increased compared to controls. Strikingly, old *Irs2^{-/-}* and *Blrs2^{-/-}* mice displayed the opposite response to refeeding; the orexigenic neuropeptides increased while POMC decreased. *Daf16*, a transcription factor of the forkhead family (orthologous to mammalian Foxo, Fkhr1, and Afx) acts in Insulin/IGF-1 pathways and influences life span in *worm*. Foxo is a target for Sirt1, a homolog of Sir2 deacetylase which is activated by energy depletion. Sirt1 and Foxo1 are highly expressed in the hypothalamus of old *Irs2^{+/-}* and *Blrs2^{+/-}* mice during fasting and after the 2 hr-refeeding following starvation, whereas their expression is comparatively reduced in *Blrs2^{-/-}* and wild type mice. Thus, reduced—but not deleted—*Irs2* signaling in the brain promotes energy homeostasis and appetite regulation, which might increase longevity.