Microglial insulin signalling plays a role in the progression of dietary-induced obesity

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Background: Obesity and type 2 diabetes mellitus (T2DM) are highly prevalent metabolic disorders which are among the leading causes of death worldwide. One of the hallmarks of obesity and T2DM is insulin resistance. Microglia – the resident immune cells in the brain responsible for keeping a healthy microenvironment for neurons to survive and function, have been shown to get activated by an obesogenic diet. Microglia express insulin receptors, however, we have very limited understanding of the involvement of microglial insulin signaling in the pathogenesis of obesity and T2DM. We hypothesize that reduced insulin signaling affects microglial immune function, which could ultimately result in dysfunction of neighboring neurons and impaired CNS control energy homeostasis.

Methods: We induced microglia-specific knock-down of the insulin receptor gene *in vivo* in $InsR^{fl/fl}$-$Cx3Cr1^{CreERT2}$ mice (InsR-KD). Male and female InsR-KD mice and $InsR^{wt/wt}$-$Cx3Cr1^{CreERT2}$ controls (InsR-WT) were fed with high-fat diet (HFD) or Chow diet for 10 weeks. Animals were perfused and fixed in paraformaldehyde. Coronal slices were used to evaluate microglial cell number and primary branching in the arcuate nucleus of the hypothalamus. Statistical analysis was performed with one- or two-way ANOVA. Data are presented as mean±SEM.

Results: Following 10 weeks of HFD, both male and female mice showed higher body weight (BW) gain in InsR-WT and InsR-KD animals, compared to the respective control group ($p<0,0001$). We observed no difference between in InsR-WT and InsR-KD animals in males and females fed Chow or HFD. We found no difference in number of microglial soma in any of the groups, however we found a reduced number of primary projections in InsR-KD animals, compared to InsR-WT, irrespective of the sex or diet.

Conclusions:
We observed a decrease in microglial primary projections in InsR-KD, compared to InsR-WT animals, which could be indicative of higher microglial activation in the absence of microglial insulin signaling.