Negr1 adhesioonimolekuli mõjud metaboolsetele häiretele

Negr1 kuulub IgLON perekonna neuraalsete adhesioonimolekulide hulka (koos Lsamp, Ntm, Opcml ja IgLON5-ga). Ülegenoomsetes GWAS uuringutes on NEGR1 geen seostunud tugevalt nii psühhiaatriliste häirete (Cross-Disorder, 2019) kui kehakaalu (Speliotes et al, 2009) fenotüüpidega. Füsioloogia osakonnas oleme varem näidanud, et Negr1 väljalülitamine muudab hiirte metaboolset profiili (Kaare et al, 2022), seetõttu on käesoleva projekti eesmärgiks selgitada millised molekulaarsed mehhanismid on Negr1 puudulikkusega hiirte muutunud metaboolse profiili taga. Joo et al (2019) on näidanud, et Negr1 puudulikkusega hiirte rasvkoes (gonadal adipose tissue) on Adiponektiini tase madalam. Madal adiponektiin selgitaks paljusid Negr1 hiirel esinevaid fenotüüpe. Adiponektiin indutseerib normaalselt rasvhapete oksüdatsiooni (Negr1 mutantidel esineb vastupidine protsess- rasvhapped pigem kuhjuvad) ning vähendab glükoneogeneesi (Negr1 mutantidel, eelkõige isastel, on oluliselt tõusnud glükoneogenees, mis väljendub eriti selgesti rasvase dieedi korral). Seetõttu Negr1 osalus Adiponektiini regulatsioonis saab olema esimene planeeritava teemaga seotud hüpotees.

Effects of the Negr1 adhesion molecule on metabolic disorders

Negr1 is a member of the IgLON family of neural adhesion molecules (together with Lsamp, Ntm, Opcml and IgLON5). In cross-sectional GWAS studies, the NEGR1 gene has been strongly associated with both psychiatric disorders (Cross-Disorder, 2019) and body weight (Speliotes et al, 2009) phenotypes. In the Physiology Department, we have previously shown that knocking out Negr1 alters the metabolic profile of mice (Kaare et al, 2022), therefore the aim of this project is to elucidate the molecular mechanisms behind the altered metabolic profile of Negr1 deficient mice. Joo et al (2019) have shown that Negr1 deficient mice have lower levels of adiponectin in the gonadal adipose tissue. Low adiponectin would explain many of the phenotypes present in Negr1-deficient mice. Adiponectin normally induces oxidation of fatty acids (the opposite process occurs in Negr1 mutants - fatty acids tend to accumulate) and reduces gluconeogenesis (Negr1 mutants, especially males, have significantly increased gluconeogenesis, which is particularly pronounced on a high-fat diet). Therefore, the involvement of Negr1 in the regulation of adiponectin will be the first hypothesis related to the planned topic.

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