OBJECTIVES/SPECIFIC AIMS: The overall objective of this proposal is to establish and modulate the inflammatory profile of individuals across the spectrum of multiple sclerosis (MS), with a focus on determining the potential of interleukin 4-induced protein 1 (IL4I1) as a possible marker of progression and modulator of inflammation in human blood samples. METHODS/STUDY POPULATION: The proposed experimental approach involves isolating plasma and peripheral blood mononuclear cells (PBMCs) from individuals across the spectrum of MS phenotypes, and analyzing these samples primarily by quantitative polymerase chain reaction (qPCR) and enzyme-linked immunosorbent assay (ELISA) methods. Specifically, study groups include: (1) actively relapsing-remitting MS (a-RRMS), (2) non-actively relapsing-remitting MS (n-RRMS), (3) non-active secondary-progressive MS (SPMS), (4) other autoimmune diseases (OAD), (5) healthy controls (HC). RESULTS/ANTICIPATED RESULTS: We expect that IL4I1 treatment increases regulatory cytokines (eg, IL10, TGFβ) expression while decreasing Th1 and Th17-derived cytokines (IFNγ, IL17), as well as increasing relative composition of regulatory cells (Th2, Treg, M2) as compared with Th1, Th17-derived cytokines (IFNγ, IL17), which is lost in SPMS.

Antipsychotic-induced weight gain arises, in part, from alteration of feeding circuitry in the lateral hypothalamic area
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OBJECTIVES/SPECIFIC AIMS: To demonstrate that olanzapine recapitulates the effect of increased lateral hypothalamic (LH) GABAergic activity in the DRN and the DBB. This will provide a potential neural substrate for the observed increase in consumption of food and weight gain. METHODS/STUDY POPULATION: We will identify the behavioral phenotype of stimulating these same projections using optogenetic techniques. (3a) Identify the behavioral phenotype of mice possessing cre-loxp-dependent knockout (KO) of LH GABAergic activity, DRN serotonergic activity, and inhibition of DBB cholinergic activity. (3b) Using these mice, we will establish behavioral response to olanzapine in ad libitum feeding and fast-refeeding condition. (4) Using baseline and post-treatment body mass index (BMI), PANSS, and side effect profile scores from a recently completed prospective cohort study of treatment-naive schizophrenic patients receiving atypical antipsychotics for 1 year, we will sequence multiple single nucleotide polymorphisms and explore the correlation of serotonergic, dopaminergic, and cholinergic receptor mutations with the increase in BMI and changes in PANSS score and side effect scores. RESULTS/ANTICIPATED RESULTS: (1) Our preliminary data indicates that the LH exclusively sends GABAergic input to the DBB, and the large majority of its projections to the DRN are GABAergic. (2) We have identified that stimulating LH > DBB projections produces intense feeding and drinking behavior, a real-time place preference for laser stimulation, and a conditioned place preference for laser stimulation. Preliminary data shows that the LH- > DRN also produces feeding behavior. (3a) Our lab has demonstrated that transgenic mice with LH-specific GABA release KO are smaller, have increased anxiety-like behaviors such a repetitive grooming and open field aversion, and have reduced feeding after fasting conditions. We expect the DRN serotonergic KO mice to have increased body weight and reduced anxiety-like behaviors. (3b) Our pilot study demonstrated that the LH GABA KO mouse administered olanzapine have a greater consumption of food over 1 hour than controls (n = 7, 5, respectively: p = 0.08). DRN serotonergic KO mice and mice with inhibition of choline will have an increased baseline feeding behavior, but will not be affected by olanzapine. (4) We believe that SNPs in serotonergic receptors such as SHT2C, and those affecting dopaminergic and cholinergic receptors, will be more common in schizophrenic patients with increased BMI than those without. Further, we believe that a reduction in the PANSS items reflecting anxiety and aversiveness will correlate with increased BMI, since we