27 PRENATAL NAP+SAL PREVENTS DEVELOPMENTAL DELAY IN A DOWN SYNDROME MOUSE MODEL BY ALTERING NMDA AND GABA RECEPTOR SUBUNITS

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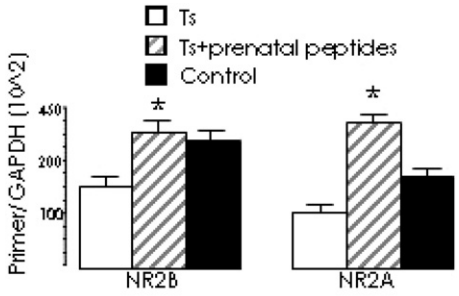
OBJECTIVE: Down Syndrome (DS) is the most common cause of mental retardation. Previously, we showed prenatal treatment with neuroprotective peptides, NAP+SAL, prevented developmental milestone delay in the Ts65Dn mouse model of DS. (Toso SMFM 2007) NMDA and GABA receptor subunits: NR2A, NR2B, GABA-Aα5 and GABA-Aβ3, are critical for the regulation of long term potentiation (LTP), the electrophysiologic model of learning. We sought to delineate if the prevention of developmental delay is mediated through alterations in the NR2B, NR2A, GABA-Aα5 and GABA-Aβ3 receptor subunits.

STUDY DESIGN: Pregnant Ts65Dn mice were treated on gestational days 8-12 with placebo or NAP+SAL. Pups were genotyped as trisomic (Ts) or euploid (control) resulting in 3 groups: Ts+placebo (n=4), Ts+NAP+SAL (n=3), control+placebo (n=4). Calibrator-normalized rt-PCR was performed using primers for NR2A, NR2B, GABA-Aα5 and GABA-Aβ3 with GAPDH standardization. Samples were run in duplicate. Statistics included ANOVA and Fisher PLSD with $P<0.05$ as significant.

RESULTS: NR2A, NR2B and GABA-Aβ3 levels were decreased in Ts vs control (all $P<0.05$). Prenatal NAP+SAL increased NR2A, NR2B and GABA-Aβ3 to levels similar to control, significantly higher than Ts (all $P<0.05$). No significant difference was found in GABA-Aα5 levels.



NR2B and NR2A Expression

NR2B and NR2A Expression

CONCLUSION: Prenatal administration of NAP+SAL at a critical point in gestation has long lasting effects as it increases NR2A, NR2B and GABA-Aβ3 expression in adult Ts offspring to levels similar to wild type controls. Prevention of alteration in these NMDA and GABA receptor subunits may, in part, explain the mechanism behind the prevention of developmental milestone delay in the mouse model of DS.

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28 SIGNIFICANT INTERACTION BETWEEN GENETIC VARIANTS IN PRETERM BIRTH ASSOCIATE WITH AMNIOTIC FLUID PROTEIN CONCENTRATIONS AND RACIAL DISPARITY

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OBJECTIVE: We hypothesize that unexplained racial disparity in spontaneous preterm birth (PTB) between African Americans (AA) and Caucasians (C) is related to how genetic variations in inflammatory pathway genes affect protein concentrations of cytokines that associate with pregnancy outcome. This study analyzed the association of 200 single nucleotide polymorphisms (SNPs) in 14 cytokine (inflammatory and anti-inflammatory), cytokine receptor genes and concentrations of 3 cytokines in the amniotic fluid (AF) that were reported to be associated with PTB.

STUDY DESIGN: Samples consisted of AA and C cases (PTB) and controls (term birth) for which both cytokine and maternal and fetal genotype data were available. Analyses were performed with genotype, case, and maker-status (case/control) interaction in the model for cytokine concentrations. ANOVA was performed with cytokine concentrations and marker, status and maker-status interaction as covariates.

RESULTS: AF IL-1β was higher in AA caseswhereas IL-8 was higher in C cases compared to the respective controls. No difference in IL-10 concentration was seen in either race. In C, very few interactions of genetic variants and pregnancy outcome were associated with AF cytokine concentrations. In contrast in AA, multiple variants (both maternal and fetal) showed significant interactions with pregnancy outcome for cytokine concentrations.

CONCLUSION: Our data indicate racial disparity in genetic regulation of cytokines concentrations. Genotypes were associated with AF cytokine concentrations in AA, but this effect is minimal in C. Interestingly, in both races, cytokine concentrations were more associated with variations in cytokine receptor and receptor antagonist genes than cytokine genes itself suggesting indirect regulation of cytokine functions in PTB.

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29 MATERNAL AND FETAL GENETIC ASSOCIATIONS WITH PRETERM DELIVERY

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OBJECTIVE: To determine genetic risk factors for PTD within 159 selected candidate genes in different PTD pathways.

STUDY DESIGN: The study consisted of 430 maternal DNA samples (213 cases, 217 controls) and 425 fetal DNA samples (209 cases, 216 controls) nested within the Norwegian Mother Child Cohort study. We studied 1453 markers from the 159 genes selected.

RESULTS: For maternal samples the most significant association was a marker (rs2472) in the collagen, type 1, alpha-2 (COL1A2) gene (allelic p-value=1.14x10-3, genotypic p-value=1.09x10-3). The odds ratio (OR) for this SNP was 0.31 (95% CI 0.15-0.64, p-value=0.001) for a recessive model. Haplotype analysis of this gene revealed multiple significant haplotypes, the strongest being a 3 marker haplotype (p=0.003). This gene is involved in the extracellular matrix (ECM) receptor interaction pathway; additionally there were significant associations in 3/4 other genes involved in this pathway. Perturbations in this pathway may lead to ECM degradation, myometrial activation and eventually PTD. In fetal samples the most significant association in fetal samples was a marker (rs6434222) in the tissue factor pathway inhibitor (TFPI) gene (allelic p-value=7.88x10-5, genotypic p-value=1.40x10-4). The OR for this SNP was 2.56 (95%CI=1.60-4.10, p-value<0.001) for a recessive model. Haplotype analysis of this gene revealed several significant associations, the most significant being a 4 marker haplotype (p-value 2.6x10-4). This marker is part of the complement and coagulation pathway which is important in decidual hemorrhage, a primary pathway of PTD. Additionally, there were 4/12 other genes in this pathway with significant associations.

CONCLUSION: This study identified several genes associated with PTD and maternal and fetal pathway breakpoints contributing to PTD.

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