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Conflict of interest

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Effects of maternal immune activation using poly (I:C) on the dendritic morphology of primary cortical cells

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Background: There is a link between maternal infections and neurodevelopmental disorders (NDDs) in the offspring via the maternal–placental–axis, the so-called maternal immune activation (MIA) [1]. Studies indicate that patients with psychiatric NDDs (e.g. schizophrenia (SZ), autism spectrum disorder (ASD)) show alterations in brain morphology [2] and sex differences in symptoms [3]. However, alterations of brain development in MIA embryos during gestation and potential sex-specific effects during this period have not yet been investigated.

Objectives: This study analysed (a) the morphology of neuronal dendrites and (b) identified potential sex-specific differences on these alterations in primary neurons derived from MIA embryonic cortices.

Methods: The viral mimetic polyinosinic:polycytidylic acid [poly(I:C)] (2.5 or 5 mg/kg) was injected intravenously in pregnant C57Bl/6J dams on gestational day (GD) 9. The control group received injections with 1xPBS (0 mg/kg). Embryos were extracted on GD 18 and primary cortical neurons were cultured with separate cultures for cortices from male and female embryos. Neurons were sparsely labelled by CRISPR-Cas9 based insertion of GFP into the Camk2a gene. After two weeks in culture, cells were fixed and labelled using immunofluorescent staining for neuronal spines (GFP) and dendrites (MAP2). Neurons were imaged with an inverted fluorescent microscope with a 20x objective (Axio Observer Z1). Dendrites were traced and analysed using the "Simple Neurite Tracer" (SNT) plugin in ImageJ. Data were statistically analysed by analysis of variance (ANOVA) with a significance threshold of $p<0.05$.

Results: The neurons from embryos of 5 mg/kg poly(I:C) treated dams showed significantly higher number of total, secondary, and tertiary dendrites compared to neurons from the 0 mg/kg and 2.5 mg/kg groups ($p<0.001$). Similarly, the length of all primary, secondary, and tertiary dendrites was significantly increased in the 5 mg/kg group (sum: $p\leq0.007$, average: $p\leq0.045$). Moreover, the average as well as the total length of primary dendrites were significantly longer in neurons from female than male embryos ($p\leq0.038$). This effect was independent of poly (I:C) treatment. Sholl analysis revealed significantly increased dendritic field radius, maximum intersections, and sum of intersections in the 5 mg/kg group compared to the other groups ($p\leq0.004$). No significant differences between the 0 mg/kg and 2.5 mg/kg groups were found ($p>0.05$).

Conclusion: The findings of this study contrast with those from our preliminary in situ investigations in Golgi-Cox stained brains of adult MIA offspring, showing shortened dendrites. However, both studies showed an increased number of dendrites in the 5 mg/kg poly(I:C) group [4]. Altogether, this may indicate that more severe alterations in the dendritic branching in offspring are tied to the high viral loads in susceptible mothers. Moreover, dendritic length may increase with high viral loads before birth, due to active neurogenesis in the early gestational period but could change later in life. Finally, our findings show that the offspring's sex only has a minor influence on dendritic growth during gestation.

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Nutrient deficiency and astrocyte starvation in patients with Alzheimer's disease

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Background: Patients with Alzheimer's disease (AD) are known to have a neurodegenerative disorder manifested by a progressive loss of brain cells that leads to memory decline, thinking problems and other dysfunctions. Amyloid-beta (Aβ) peptides are believed to be cause for AD. However, Aβ peptides present in both the cognitive normal (CN) and AD brains [1]. Furthermore, much of evidence supports that monomeric peptides do not cause cell death under a variety of experimental conditions. The biological role of Aβ peptides in Alzheimer's patients remains to be determined. It has been suggested that AD is associated with hypometabolic disorder [2]. AD patients often have unintentional weight loss [3]. The incidence rate of diabetes mellitus is high in AD patients [4]. Recently, anti-diabetic drugs have been found to have a clinical value for AD treatment [5]. Based on these studies monomeric Aβ peptides could be involved in cell metabolic activity possibly by regulating nutrient uptake to brain cells.

Objectives: The present study had two main objectives First, determine effect of monomeric Aβ peptides on glucose uptake into cytosol and ATP synthesis; second, compare the effect of Aβ peptides with cell starvation by depriving nutrients in culture medium.

Methods: Human immortal astrocytes (ATCC# CRL-1620) were used to test the nutrient deficiency and cell starvation hypothesis. Monomeric Aβ peptides were obtained by dissolving peptide powders to 0.5%DMSO. Briefly, cells were cultured with Dulbecco's modified Eagles's medium (DMEM) supplemented with 10%FBS. Two hours after seeding in plates, cells were treated with three different peptides, specifically Aβ1-42 Aβ1-40, or Aβ25-35. In separate experiments, cells in the medium were deprived from glucose, pyruvate and glutamine. The next day, cell cytosol was extracted. Cytosol glucose and ATP were determined with HPLC coupling with UV detection. Data were analyzed with ANOVA or t-test, and statistical significance set <0.05.

Results: We found that cytosol glucose was dose-dependently inhibited by monomeric Aβ peptides at concentrations of 1-50mM. Aβ1-42 and Aβ1-40 were equipotent. In contrast, the inhibitory effect was low for Aβ25-35. Cytosol ATP was also dose-dependently reduced by Aβ peptides. The inhibitory potency for ATP synthesis was similar to that for inhibiting glucose uptake. However, changes in glucose were not proportional to reduction in ATP. Lastly, we determined levels of cytosol glucose, and ATP extracted from starving cells. Cytosol glucose was depleted within 30 min. Despite this, ATP was not significantly reduced until 2hrs later. No cell death detected while glucose was completely depleted for 2hrs.

Conclusion: Our results revealed that monomeric Aβ peptides inhibit glucose uptake into astrocytes resulting in ATP reduction in cells. The effect of Aβ peptides is very similar to cell starvation. Thus, we conclude that Aβ peptides cleaved from amyloid procure proteins (APP), at micromolar concentrations, act as a glucose uptake inhibitor. Therefore, cells likely undergo nutrient deficiency and