40. NEW INSIGHTS ON THE ROLE OF NEUROINFLAMMATION IN SCHIZOPHRENIA PATHOPHYSIOLOGY FROM POST MORTEM AND ANIMAL STUDIES

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Overall Abstract: Recent years have witnessed an explosion of clinical and preclinical effort aimed at understanding the involvement of neuroinflammation in schizophrenia (SCZ). The aim of this symposium is to present new and complementary data from human post mortem brain tissue and the rodent maternal immune activation (MIA) model, which together support the involvement of neuroinflammation in SCZ.

Tertia Purves-Tyson will present the first post mortem evidence that neuroinflammation in SCZ extends to the midbrain, a region critical for psychosis and cognitive deficits. She will show that: 1. gene expression of multiple pro-inflammatory cytokines is increased in the post mortem substantia nigra in SCZ compared to controls, in whose brains no such changes are seen; 2. as in the cortex, gene expression changes were found only in a subset of cases (~50%) of the SCZ cohort. She will also explore whether previously identified decreases in dopamine-related transcripts (transporters and receptors) in the substantia nigra in SCZ brains are related to the inflammation status. Ulrike Weber will show in the MIA model that the inflammatory changes identified in the midbrain of patients with SCZ may have a prenatal origin stemming from exposure to inflammation-related environmental insults. Remarkably mimicking the post-mortem data, MIA in mice increased brain pro-inflammatory cytokine gene expression, in not only the prefrontal cortex, but also in the ventral midbrain, and, similarly to humans, only in ~50% of offspring. She will also explore the relationship between changes in immune-related and dopamine-related gene expression in this brain region of MIA offspring. Anthony Vernon will show that MIA exposure on GD15 in rats leads to increased microglia density and soma size in the adult rat striatum and cingulate cortex. Strikingly, chronic haloperidol treatment at clinically comparable doses in adulthood interacts with prenatal MIA exposure, leading to further increases in both microglia density and soma size in both the striatum and frontal cortex. These data suggest adult antipsychotic exposure may increase neuroinflammation in the MIA model. Ina Weiner will report on the effects of subchronic low-dose risperidone treatment (RIS) in adolescence on neuroinflammation in MIA offspring, quantified using radiolabeled [3H]PK11195, a selective TSPO ligand and clinically comparable index of putative microgliosis. Compared to controls, [3H]PK11195 binding was increased in the hippocampus and frontal cortex of adult males and the hippocampus of females, with no changes in adolescence, partially mirroring the results of [11C]PK11195 in-vivo PET in SCZ patients. These increases were prevented in MIA offspring after RIS administration in adolescence, in parallel with prevention of brain volumetric reductions and cognitive deficits. Early intervention with RIS may decrease neuroinflammation and potentially underlie the preventive effects of RIS in the MIA model.

Taken together, these data support the involvement of neuroinflammation in SCZ and MIA model rodents. In particular, they suggest that high inflammatory profile, while distinguishing SCZ/MIA brains from control brains, may characterize only subsets of patients/MIA offspring, or may exist in all individuals but on an on-off basis, implying that preventive and current treatments may interact with neuroinflammation. Indeed, while APDs given to adult symptomatic offspring, interact with neuroinflammation to increase it further, early treatment with APDs in nonsymptomatic offspring prevents neuroinflammation. Evaluation of fluctuations in neuroinflammation over the lifespan and their interactions with treatment effects is a next step.

40.1 INFLAMMATORY CYTOKINES ARE ELEVATED IN THE MIDBRAIN IN SCHIZOPHRENIA

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Background: Neuroinflammation is attractive as a candidate mechanism contributing to schizophrenia neuropathology. In ~40% of people with schizophrenia, pro-inflammatory cytokines are elevated in post mortem prefrontal cortex and in peripheral blood of living patients. Dopamine dysregulation contributes to cognitive deficits and psychosis and cytokines can increase dopamine production, yet post mortem midbrain cytokine transcripts have not been examined. We hypothesised that gene expression of inflammatory markers will be elevated in the midbrain of a subset of people that suffered with schizophrenia during their lives.

Methods: Pro-inflammatory cytokine mRNAs for interleukin (IL) 1β, IL6, IL6 signal transducer (IL6ST), IL8, 1L18, tumor necrosis factor (TNF) α, SERPINA3, and the microglia marker, allograft inflammatory factor 1 (AIF1), were examined by qPCR in the midbrain from 28 schizophrenia cases and 29 healthy controls. All patients were on antipsychotics at time of death and antipsychotic medication was converted to chlorpromazine (CPZ) equivalents. Inflammatory subgroups were defined using two-step cluster analysis of cytokine mRNAs on the entire cohort. Chi-squared was used to test if the number of individuals in the inflammatory groups differed on the basis of diagnosis. Student's t-tests or ANCOVA were used to detect diagnostic differences and differences between inflammatory/diagnosis subgroups. Student's t-tests were used to compare CPZ equivalent doses in the low and high inflammation schizophrenia groups.

Results: SERPINA3, IL1β, IL6 mRNAs were increased by more than 150% and IL6ST mRNA by 17% in the midbrain from schizophrenia patients compared to controls ($F>4.0$, $p<0.0001$–0.05), whilst IL8, IL18 and AIF1 mRNAs were unchanged ($p>0.05$). Cluster analysis revealed 13 individuals as high inflammation and 44 as low inflammation. All 13 individuals in the high inflammatory group were schizophrenia cases and the remaining 15 schizophrenia cases and all the control cases were low inflammation ($\chi2=57.0$, $P<0.0001$, $N=57$). SERPINA3, IL6, IL1β and TNFα mRNAs were all increased in the high inflammation/schizophrenia compared to control and low inflammation/schizophrenia groups ($p<0.002$–0.05). AIF mRNA was not changed by diagnosis, but was increased in the high inflammation/schizophrenia compared to the low inflammation/schizophrenia group ($p=0.015$). The schizophrenia/high inflammation group received higher lifetime, daily and last CPZ equivalent doses ($t(20–26)<-2.7$, $p<0.05$) compared to the schizophrenia/low inflammation group.

Discussion: Inflammatory markers were elevated in the midbrain in ~50% of schizophrenia cases, whilst no controls were classified as high inflammation. This data suggests that increases in pro-inflammatory cytokines extend to midbrain regions and may contribute to the neuropathology of the disorder by contributing to dopamine dysregulation. PET studies relate increased microglia activity to at-risk symptom severity in medication naïve people at ultra high risk for schizophrenia, we suggest that the higher dose of antipsychotics in the high inflammation group along with increased microglial marker may indicate that these patients were sicker and thus, required more medication, rather than antipsychotics increasing inflammatory markers. In conclusion, increased cytokine transcripts indicate a neuroinflammatory process in the midbrain in some people with schizophrenia. Future post mortem studies will explore whether previously identified changes in dopamine-related transcripts in the midbrain in schizophrenia are altered according to inflammatory state.