EFFECTS OF THE PPAR-ALPHA AGONIST FENOFIBRATE IN AN IMMUNE-MEDIATED NEURODEVELOPMENTAL MODEL OF PSYCHOSIS

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Prenatal immune system activation is associated with a later risk to develop neuropsychiatric disorders with a supposed neurodevelopmental origin, such as schizophrenia. Hence, immune response factors in pregnant dams, at specific ages of pregnancy, affect offspring brain maturation, contributing to the emergence of pathological phenotypes at adulthood. Several variables can also have impact on the pathological outcome, such as sex differences, age and genetic background. Evidence suggests that ventral tegmental area (VTA) dopamine (DA) neurons and their target regions play key roles in the neuropathological mechanisms underlying psychoses. However, it remains to be fully established how DA transmission is impacted by maternal immune activation (MIA) models of schizophrenia and whether sex differences moderate this impact. Moreover, pharmacological strategies to reduce the risk of neurodevelopmental disorders are lacking. The role of peroxisome proliferator-activated receptors-alpha (PPARα), a member of a nuclear receptors family widely expressed in the CNS, is attracting a special interest. Activation of PPARα has been found to regulate gene expression involved in inflammation and neuroprotection. Therefore, we investigated if PPARα activation, with the clinically available agonist fenofibrate, prevents MIA-related neurodevelopmental disturbances.

On these bases, we used an immune-mediated neurodevelopmental disruption model, which mimics a viral infection and recapitulates behavioral and cognitive abnormalities relevant to psychiatric disorders in offspring. Pregnant dams were injected at gestational day 15, comparable to the second trimester of human pregnancy, with the proinflammatory cytokine inductor polyriboinosinic-polyribocytidilic acid [poly(I:C), 4 mg/kg i.v.] or vehicle. Animals were fed from GD 8 to GD 18 with either a standard diet or fenofibrate-containing diet (0.2% w/w). The offspring were behaviorally assessed at adulthood for deficits in sensorimotor gating, commonly described in human schizophrenic patients. Pre-pulse inhibition (PPI) of acoustic startle reflex was examined at postnatal day 60-70. Subsequently, in vivo electrophysiology was carried out in adult offspring to assess DA neuron activity in the VTA. All experiments were performed in both male and female offspring.

Poly(I:C)-treated adult male rats displayed impairments in PPI when compared to controls. Notably, poly(I:C) prenatal exposure did not affect this parameter in female offspring.

Electrophysiological experiments showed that DA neuron activity was disrupted by poly(I:C) treatment during pregnancy in male but not in female offspring. DA neurons recorded from male offspring of poly(I:C)-treated dams displayed disrupted synaptic functions, a lower frequency and a reduction in their number when compared to controls. In addition, burst activity was significantly

reduced. Consistent with the lack of PPI disruption, no differences in electrophysiological parameters were detected in female offspring.

Detrimental effects on DA neuron activity in males were prevented by the fenofibrate treatment during pregnancy.

Our data provide evidence of altered behavior and disrupted DA transmission following exposure to maternal immune activation in male but not in female rats. These findings are consistent with human epidemiological studies showing higher prevalence of psychoses in males versus females and underscore the need to investigate sex differences in animal models of psychiatric disorders. Our study highlights also that PPAR-α activation might represent a promising target to reduce risk in vulnerable individuals.