P-02.009 Prenatal immune challenge causes frontal-subcortical proteome changes relevant to schizophrenia and autism

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Objective: Maternal immune activation (MIA) during prenatal life increases risk of neurodevelopmental disorders including schizophrenia and autism. Schizophrenia and autism cause alterations in fronto-striatal circuits, but the molecular basis is unclear. In this study we experimentally tested the impact of MIA on adult prefrontal and striatal proteome.

Methods: A conventional MIA mouse model, generated by administering the viral analogue PolyI:C or saline (control) intravenously on gestation day 9, was adopted. Striatal and prefrontal cortex (PFC) proteomes of 4 male and 3 female MIA and control adult mice were compared using advanced 2-dimensional differential in-gel electrophoresis (2D-DIGE).

Results: In striatum, around 1500 spots were detected by DeCyder Differential In-gel Analysis (DIA) module. After standard protein exclusion filtering, around 1300 spots were included for Biological Variation Analysis (BVA). In PFC around 1800 spots were detected and 1300 spots were included for BVA module. Independent Student t-tests revealed that in the striatum, 11 spots showed up-regulation and 4 spots showed down-regulation in polyI:C group. Nine protein spots were identified by MALDI-TOF mass spectrometry. In polyI:C PFC region, 10 spots were up-regulated, 7 spots down-regulated and 9 identified by MALDI-TOF mass spectrometry. The expression of proteins altered in PolyI:C mice included dual specificity mitogen-activated protein kinase kinase 1 (MEK), eukaryotic initiation factor (eIF) 4A-II, creatine kinase (CK)-B, L-lactate dehydrogenase (LDH)-B, WD repeat-containing protein and NADH dehydrogenase in the striatum; and guanine nucleotide-binding protein (G-protein), 14-3-3 protein zeta/delta (KCIP-1), alpha-enolase, olfactory maker protein and heat shock protein (HSP)60, and 90-beta in the PFC.

Conclusion: The present data fits with emerging evidence that key components of critical converging intracellular pathways including MAPK, PTEN, mTOR and FMRP are altered in neurodevelopmental conditions which may open fresh avenues for capturing biomarkers and novel treatment targets for neurodevelopmental conditions.

Policy of full disclosure: None.

P-02.010 Antidepressant-like effect of phytoestrogen daidzein in ovariectomized rats in the forced swimming test

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Objective: Numerous reports demonstrate the potency of phytoestrogens to ameliorate physical and emotional alterations in ovarian dysfunction and permanent absence of ovarian hormones (DAnna et al., 2007). The aim of the present study was to determine the antidepressant-like effects of different doses of phytoestrogen daidzein in the ovariectomized (OVX) rats submitted to the forced swimming test (FST), and its effect was compared with a clinically effective antidepressant, clomipramine.

Methods: OVX female Wistar rats were used in all experiments. Two weeks later after surgery rats were treated with vehicle, daidzein (0,1, 0,5 and 1,0 mg/kg, i.p.) or clomipramine (50.0 mg/kg, i.p.) chronically for 14 days before the forced swimming test (FST) and open field test (OFT). Immediately after the FST and OFT, hormonal assay for estradiol (E2) and follitropine (FSH) levels in the blood was performed. The data wee analyzed by one-way ANOVA with Dunnett's post-hoc test.

Results: In the FST, daidzein (0.5 and 1.0 mg/kg) and clomipramine significantly decreased immobility behavior in OVX females as compared to the control group ($p < 0.05$). In addition, daidzein failed to change swimming time or struggling time in the OVX rats in the FST. In the OFT, daidzein (0.5 and 1.0 mg/kg) increased frequency of rearing and duration of grooming as compared to the control group ($p < 0.05$). The hormonal assay results demonstrated the increased E2 levels and decreased FSH levels in the blood in the group treated with daidzein as compared with OVX rats. The results of this study provide evidence that phytoestrogen daidzein exerts antidepressant-like effect in rats with deficiency of ovarian hormones in the FST.

Conclusion: In conclusion, phytoestrogen daidzein produces antidepressant-effect in female rats with absence of ovarian hormones in the FST, supporting the hypotheses that phytoestrogens could be used to ameliorate depression associated with ovarian dysfunction or menopause.

Policy of full disclosure: None.

P-02.011 Synergistic interaction between prenatal immune challenge and peri-pubertal stress in the disruption of adult behavioral functions relevant to schizophrenia

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Objective: Converging evidence from human epidemiological studies and parallel experimental investigations in animals indicates that prenatal exposure to infection may be a relevant environmental risk factor for schizophrenia and related disorders. However, if prenatal infection does indeed play a significant role in the etiology of schizophrenia, then it likely does so by interacting with other genetic and/or environmental susceptibility factors. Besides prenatal infection, exposure to stressful situations in peri-pubertal stages of life has been repeatedly suggested to represent a significant postnatal environmental factor in the development of psychotic disorders. Against this background, the present study was designed to test the hypothesis whether prenatal viral-like immune challenge may synergistically interact with peri-pubertal stress to facilitate the emergence of schizophrenia-like behavioral abnormalities in adulthood.

Methods: We combined a well established mouse model of prenatal (gestation day 9) immune challenge by the viral mimic Poly[I:C] with a model of exposure to peri-pubertal stress induced by a 5-days variable stress protocol applied in peri-puberty (postnatal days 30 to 35).

Results: We found that peri-pubertal stress led to significant impairments in sensorimotor gating in the form of prepulse inhibition (PPI) disruption and blunted exploratory activity in a novel environment specifically in animals which had been subjected to prenatal Poly[I:C]-induced immune challenge at low intensity (1 mg/kg, i.v). Neither prenatal Poly[I:C] treatment at the chosen dose alone nor peri-pubertal stress alone induced such behavioral abnormalities.

Conclusion: Our findings support the biological plausibility for synergistic interactions between prenatal immune challenge and postnatal stress in the precipitation of brain dysfunctions relevant to schizophrenia. In accordance with an environmental two-hit model of schizophrenia etiology, prenatal immune challenge may render the brain more vulnerable to postnatal stress, thereby facilitating the development of full-blown psychotic disturbances associated with schizophrenia.

Policy of full disclosure: None.

P-02.012 Inositol transporter knockout mice show a lithium-like phenotype in the amphetamine-induced hyperactivity paradigm

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Objective: Lithium (Li), the drug of choice in bipolar disorder, reduces the function of the sodium-myo-inositol cotransporter (SMIT)1 and was shown to decrease brain myo-inositol levels in rodents. Reduction in brain myo-inositol was also found in SMIT1 knockout mice (1). Homozygous but not heterozygous SMIT1 knockout mice were shown to exhibit lithium-like behavior in the pilocarpine-induced seizure paradigm and the forced swimming test (1). In rodents, chronic Li treatment results in reduced amphetamine-induced hyperactivity (2). 1)Agam G, Bersudsky Y, Berry GT, Moechars D, Lavi-Avnon Y, Belmaker RH. Biochem Soc Trans. 2009. 2) Gould TD, O'Donnell KC, Picchini AM, Manji HK. Neuropsychopharmacology 32:1321-33, 2007.

Methods: SMIT1 homozygous knockout male mice, 2.5–4.5 month old ($n = 19$) and their wildtype littermates ($n = 26$) were placed