Genetics & molecular neurobiology

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Oxidative stress – A promising candidate in explaining the neurobiology of autism spectrum disorders

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Introduction The diagnoses of autism spectrum disorders (ASDs) are based on a phenotype, characterized by impaired social interaction and communication and by repetitive and restricted interests. However, this might not represent a single clinical entity, but a behavioral manifestation of different neurodevelopmental deficits with a multifactorial etiology. Small studies have shown elevated levels of oxidative stress and lower levels of anti-oxidants in patients with ASD, and correlations with the severity of ASD. Therapies targeting oxidative stress have shown improvements regarding behavior, social interaction and verbal communication in patients with ASD, supporting the oxidative stress theory.
Objectives To evaluate the importance of oxidative stress in the neurobiology of adults with ASD.
Aims There is a need to understand the neurobiology of ASD, therefore this study analyzes the level of oxidative stress in a larger cohort of patients with ASD and compares to controls.
Methods The study includes 350 patients over 18 years of age diagnosed with ICD-10 diagnoses F84.0, F84.1, F84.5 or F84.8 and compared to gender and age matched neurotypical controls. The included probands will have their serum and plasma analyzed for levels of oxidative stress (superoxide dismutase 1 and 2, catalase, glutathioneperoxidase, malonialdehyde, thiobarbituric acid reactive substances and xanthinoxidase).
Results The preliminary results will be presented at the EPA in March 2016 in Madrid.
Conclusion With this study we aim to elucidate some of the neurobiology in ASD. This could lead to new potential targets for treatment and prevention of the disorders.
Disclosure of interest The authors have not supplied their declaration of competing interest.

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Plasma micro-RNA profiles in patients with major depressive disorder (MDD)

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Introduction Micro-RNAs (miRs) are involved in processes associated with MDD such as neural plasticity, neurogenesis, synaptogenesis and stress response. MiRs are detectable in biological fluids; however, no data is available regarding the use of plasma circulating miRs as markers of MDD, only whole blood or serum being reported so far.
Objectives We investigated plasma miR profiles as potential markers for MDD in patients treated with antidepressants.
Aims To detect and characterize differentially expressed miRs in the plasma of MDD patients, before and after treatment with escitalopram.
Methods Blood was collected from patients with MDD before and after 12 weeks of treatment. Plasma profiles of 1008 miRs were measured by real time PCR. The fold change of expression between time points was calculated and a paired *t* test was used for statistical significance. Gene targets and pathways were assessed in miRWalk2.0.
Results From 222 plasma miRs expressed, 40 were significantly different after treatment. Upregulated miRs (23) belonged to 43 pathways, down-regulated miRs (17) belonged to 46 pathways; the top 5 significant pathways identified being pathways in cancer, Wnt signalling, endocytosis, axon guidance and MAPK signalling. Six of these miRs are common to all five pathways: miR-146a-5p, miR-146b-5p, miR-221-3p, miR-24-3p, miR-26a-5p.
Conclusions Our analysis of significant changes in plasma miRs after escitalopram treatment of MDD might open new avenues for the understanding of its mode of action and its side effects. To our knowledge, this is the first study to assess miRs affected by antidepressant treatment in plasma of MDD patients.
Disclosure of interest The authors have not supplied their declaration of competing interest.

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Characterizing rare mis-sense variations of CACNA1I identified in a Swedish schizophrenia cohort

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CACNA1I ($hCa_V3.3$) encodes the $\alpha 1$ pore-forming subunit of human voltage-gated T-type calcium channels. $Ca_V3.3$ is expressed in a limited subset of neurons including GABAergic neurons of the thalamic reticular nucleus (TRN) where they support oscillatory activity essential for sleep spindle generation. *CACNA1I* is implicated in schizophrenia risk by emerging genetics including genome-wide association studies (PGC, 2014), and exome sequencing of trio samples (Gulsuner et al., 2013). In order to understand the impact of disease-associated sequence variation on the function of $Ca_V3.3$, we set out to analyze a complete set of rare mis-sense coding variations in *CACNA1I* in a Swedish cohort, including 15 variations identified in patients, 20 identified in control subjects, and 23 in both. We established a heterologous expression system of isogenic cell lines, each carrying single-copy inducible cDNA variants of $hCa_V3.3$, and evaluated their functional impact on channel function by electrophysiology, calcium imaging, and biochemistry. We found at least five coding variations impaired overall channel protein abundance, as well as whole cell current density. In addition, we identified $hCa_V3.3$ variants with altered voltage-dependence of channel activation and inactivation. Overall, we found that reduced calcium influx through $hCa_V3.3$ is associated with the group of variants identified in patients, compared to those in both patients and controls. Our findings suggest that patient-specific rare variations of *CACNA1I* may influence channel-dependent functions, including rebound bursting in TRN neurons, with potential implications for schizophrenia pathophysiology.

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