Département de psychiatrie

Centre de Neurosciences Psychiatriques

CNP SEMINAR

ANNOUNCEMENT

Tuesday September 3rd 2024, 11:00 to 12:00 am

MODELING NEURODEVELOPMENTAL ALTERATIONS IN ADHD AND THE IMPACT OF TREATMENT.

By: **Prof. Edna Grünblatt**

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Summary:
Due to its polygenic and phenotypic spectrum, attention-deficit hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder. The disorder affects over 5% of children and adolescents worldwide, with 60% persisting into adulthood. While the cause of ADHD is unknown, neurodevelopmental delays associated with Wnt-pathways, as well as subsequent oxidative stress (OS) and inflammation, suggest plausible causes. Response to Methylphenidate (MPH), a psychostimulant, is one of the highest in mental disorders, yet some do not benefit due to either a partial or no response. Nevertheless, the mechanism of action remains unclear. Evidence has demonstrated that certain patients benefit from polyunsaturated fatty acids (PUFAs), specifically omega-3. This can be related to its anti-inflammatory and anti-OS capabilities. However, there is currently no clear evidence to support this. We modeled ADHD using patient-derived induced pluripotent stem cells (iPSCs), neural stem cells (NSCs), and forebrain cortical neurons (FCNs) to exactly determine these alterations (growth, Wnt, cytokines, OS, and synaptic puncta) and treatment-specific responses. Compared to controls, ADHD cells exhibited decreased growth rates, linked to alterations in Wnt activity. These alterations are associated with personalized genetic predisposition and clinical scores, enhancing the model's clinical translation ability. Additionally, ADHD FCNs showed elevated OS and alterations in inflammatory markers. Finally, in FCNs, the evaluation of colocalizations between Synapsin-1 and Homer-1 (proteins located at the pre- and post-synaptic sites, respectively) demonstrated an increased synaptic connectivity in individuals with ADHD. MPH was found to reduce these cellular alterations, while omega-3 was partially beneficial. However, this benefit was not specific to ADHD patients; it also affected control lines. Notably, the response to MPH was only detected in clinically responsive patients, suggesting specific mechanisms. Overall, our findings contribute to explaining ADHD's etiology and treatment mechanisms in patient-specific neural cell models, paving the path to novel approaches, preventive measures, and discoveries of new therapeutic targets.

Invited by: paul.klauser@chuv.ch

Short Bio:
Prof. Edna Grünblatt heads the Translational Molecular Psychiatry research in the Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric University Hospital Zurich (PUK), Switzerland. Additionally, she serves as the Chair of the ECNP iPSC platform for Neuropsychiatry Network. The primary area of her research is neurodevelopmental mental disorders, with a particular focus on attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), psychosis (including schizophrenia), and early onset obsessive-compulsive disorder (OCD). Her group is currently carrying out investigations on the potential molecular and cellular link between ADHD and Alzheimer's disease across the lifetime. Her group does research in both pre-clinical and fundamental molecular neuroscience, using both approaches in translational research. The employed methodologies encompass molecular genetics, epigenetics, neuropsychopharmacology, neuronal cellular models, and biochemical analyses. Their study aims to clarify the underlying causes and mechanisms of the disorders by identifying biomarkers that may be used for early diagnosis and personalized treatment. Additionally, they seek to anticipate how patients will respond to treatment and what the consequences of the treatment will be. Currently, she has established patient-specific iPSC (induced pluripotent stem cell) neuronal modeling to enable personalized medicine, via studies of the neuronal/molecular alterations in a dish in an “ex vivo” manner. This model provides a non-invasive approach to investigating the etiopathology of neurodevelopmental disorders as well as testing drug therapy and developing new therapy approaches.

Publications:
https://scholar.google.com/citations?user=kyqpazwAAAAJ&hl=de&inst=13856427432203950092

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