UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title

Targeting the kynurenine pathway in schizophrenia: a translational approach to identify novel therapeutics and biomarkers

2)Abstract (max 500 words)

Schizophrenia is a severe mental illness and a leading cause of disability worldwide. The disease is characterized by a multifactorial etiology and complex clinical phenotype, and its underlying pathophysiological mechanisms and biological correlates remain only partially understood. Beyond dopaminergic hyperfunction, which represents the primary target of all currently available antipsychotic drugs but often fails to adequately address negative and cognitive symptoms, schizophrenia has also been associated with other central dysfunctions. At the neurochemical level, these include glutamatergic hypofunction and an altered inflammatory profile. Patients also show dysregulation of the kynurenine pathway of tryptophan metabolism, which lies at the crossroad between inflammation and glutamatergic signaling. This pathway represents a novel, potentially druggable target capable of mechanistically linking these disparate dimensions. At the neurophysiological level, EEG alterations in both resting state and task-related oscillations have been consistently observed in individuals with schizophrenia, and abnormalities in sleep architecture are now considered an integral correlate of schizophrenia pathology and a potential endophenotype of the disease. However, the mechanisms by which these alterations are individually and collectively associated with the psychopathology and cognitive impairments characterizing the illness have not been clarified yet. This PhD project is therefore aimed at further validating the kynurenine pathway as a novel therapeutic target by providing a more profound and comprehensive characterization of the interaction between these domains, with a particular focus on the intersection between inflammation, kynurenine pathway metabolism, glutamatergic dysfunction, and sleep abnormalities. Using established murine models of schizophrenia based on pharmacologically induced glutamatergic hypofunction (e.g., MK-801), we will assess the effects of inflammation and targeted pharmacological modulation of the kynurenine pathway (specifically, via the administration of targeted enzyme inhibitors such as KAT inhibitors) on sleep-wake patterns and neural activity. In vivo electrophysiology and EEG analyses will be employed to characterize neurophysiological correlates, while behavioral testing will be used to assess domains relevant to positive, negative, and cognitive symptoms. The underlying neurobiological mechanisms and potential therapeutic efficacy will be further investigated by testing whether this specific pharmacological modulation of the kynurenine pathway can effectively rescue neurophysiological and behavioral abnormalities associated with glutamatergic hypofunction, thereby establishing a strong preclinical rationale for this novel pharmacological approach.

Finally, preclinical findings will be complemented by analyses in patients with schizophrenia, by examining the associations between psychopathology, cognitive performance, sleep parameters, circulating inflammatory mediators and tryptophan-kynurenine metabolites, as well as related genetic biomarkers to guide future potential targeted therapies. This integrated and multidisciplinary approach will provide novel insights into the pathophysiology and psychopharmacology of schizophrenia. By advancing our current understanding of the interplay between inflammatory, neurochemical and neurophysiological processes, the findings from this project can contribute to identify novel biological markers for patient stratification, and support the development of innovative neuropsychopharmacological strategies centered on kynurenine pathway modulation aimed at improving clinical outcomes and quality of life in individuals with schizophrenia.