Targeting glial cells to develop novel therapeutics in neuropsychiatry

L. Steardo[1]

[1]Dept. of Physiology and Pharmacology 'Vittorio Erspamer' SAPIENZA University of Rome

The last decade has witnessed exciting and important advances in the neuroscience of mental health including the mapping of neural circuitry and neurochemical mechanisms, identification of multiple genetic loci and the application of novel technologies to both the pathophysiology and treatment of mental disorders. Despite these advances, major unmet needs remain, and mental health is experiencing a crisis in the development of new treatments, especially drug treatments. Moreover major pharmaceutical companies are even shifting drug discovery efforts away from psychiatric toward non-psychiatric disorders with well identified biological targets. Why have advances in basic neuroscience and our understanding of these diseases not allowed innovative discoveries in drug research? Several inter-related factors account for this failure. Certainly one of the most relevant to be considered is that the disease state remains based on phenomenological rather than biological categories, with limited understanding of pathophysiology. Research in the last three-four decades realized that the high heterogeneity of cell types populating the brain might have offered an invaluable source of new information on brain´s functions. Among the cell types that got increased attention in these years, glia cells in general, and astrocytes in particular, have appeared in all their multifaceted spectrum of activities. The abundant information on these cell types suggested that they serve not only a key supportive role for several brain functions, but can also become a priceless tool to specifically refine pharmacological treatments, once knowledge about their functions (or dysfunctions) becomes more available. Along this line astroglia are ultimately involved in pathogenesis of many (if not all) neuropsychiatric diseases. Further research is needed to expand our understanding of how astroglia regulate synaptic development and functioning in circuits implicated in cognition, emotion, and social functions, and how gene/environment developmental interactions could affect astrocytic functions. Another principal challenge lies in detailed characterization of remodeling of astrocytes in the disease-specific context. This is particularly important when taking in account remarkable heterogeneity and plasticity of astrocytes. Nonetheless, neuropathological and neuroimaging evidence demonstrates that in most of neuropsychiatric illnesses the astroglial atrophy and astroglial asthenia have the leading role, in contrast with other conditions in which astrogliosis prevails. In chronic diseases such as schizophrenia and major depressive disorders decrease in astroglial numbers and functional capabilities are, arguably, fundamental for pathological development being responsible for neurotransmitter imbalance and failure in connectivity within neural networks. In neurodegenerative diseases atrophic changes and astrogliosis, the latter triggered most likely by the appearance of specific lesions such as senile plaques or dying neurons, occur at the early and later stages of the pathological progression, respectively. It is therefore possible to hypothesize that neuropsychiatric diseases represent chronic astrogliopathology, which compromises glial homeostatic and defensive capabilities, and the degree and the alacrity of glio-degenerative changes contribute to the progression and outcome of these disorders. Although, by no means it can not support the notion that the removal of glial dysfunction may completely solve any problem regarding the treatment of mental illness, nevertheless this hypothesis has to be taken into account for future drug development in neuropsychiatry. Indeed, the multitude of molecules, specifically expressed by neuroglial cells and responsible for their homoeostatic and defensive functions provides alternative approaches for investigations that may open avenues to search for novel potential strategies of treatment.