Article: 1757
Topic: EPV31 - e-Poster 31: Schizophrenia

Molecular Translational Studies for Schizophrenia– Roles of Oligopeptidases and Their Substrate Neuropeptides in Clinics and Animal Models

M. Hayashi[1], C. Yonamine[1], A. Gadelha[2], A.M. Vendramini[1], M. Nering[1], V. Oliveira[1], R.A. Bressan[2], V.C. Abilio[1]

[1]Pharmacology, Universidade Federal de São Paulo, São Paulo, Brazil ; [2]Psychiatry, Universidade Federal de São Paulo, São Paulo, Brazil

Schizophrenia (SCZ) is a complex and severe chronic mental disease presenting deficits in an operational measure of sensorimotor gating and cognitive impairments. The history of delayed developmental milestones and the presence of minor physical abnormalities may represent indirect evidences of abnormal prenatal development. Premorbid cognitive, personality and social functioning deficits in patients severely affected are also reported. Among the several candidate risk genes potentially associated with SCZ via pleiotropic mechanisms and/or other genes specific to susceptibility for SCZ, the Disrupted-in-Schizophrenia 1 gene (*DISC1*) is the most studied. Interestingly, the main binding partner and effector of DISC1 protein is the Nuclear-distribution gene E homolog like-1 (Ndel1), which is an oligopeptidase capable to degrade small peptides such as bradykinin (BK) and neurotensin (NT). Both neuropeptides were implicated in SCZ, and NT was also suggested to be an endogenous antipsychotic. DISC1 binding inhibits the Ndel1 enzyme activity competing with the peptide substrates, and the described translocation of *DISC1* gene cosegregated with SCZ suggest a DISC1 and Ndel1 complex formation impairment with potential deregulation of the Ndel1 total activity. Other oligopeptidase, as Angiotensin I-Converting Enzyme (ACE), is also able to cleave these peptides. Therefore, our group is focused on measuring the oligopeptidase activity not only in clinical samples to allow the comparison between patients and health controls (HCs), but we have also performed the same measurements in plasma and different brain regions of animal models aiming to have insights into what may be occurring in the human brain based on peripheral tissues measurements. A significant lower Ndel1 oligopeptidase activity (Gadelha et al., J Psych Res 2013) and significant higher ACE activity (Gadelha and Vendramine et al., *submitted* 2014) in the plasma of SCZ patients compared to HCs were observed. Moreover, a potential association of the ACE oligopeptidase activity with the cognitive/disorganization symptoms was observed in both SCZ patients and animal models. The evaluation of the activity of these oligopeptidases in patients and animal models treated with the same antipsychotics are currently ongoing in our laboratory. The results presented here support the potential involvement of Ndel1 and ACE in SCZ, and they may contribute to the discovery of molecular biomarkers for diagnosis and/or treatment follow-up of a severe chronic mental disease as SCZ, aiming to contribute to foster the translation of basic neurobiological and behavioral research to an improved integrative understanding of psychopathology for the development of a new and/or optimized treatments.

Financial support by FAPESP, CNPq and CAPES.

https://doi.org/10.1016/S0924-9338(15)31352-3 Published online by Cambridge University Press