Abstract

Background: Group I metabotropic glutamate receptor (mGluR1 and mGluR5) allosteric modulators are currently being investigated as novel therapeutics for the treatment of neurodevelopmental disorders such as schizophrenia, autism, depression (Cleva and Olive, 2011). Recent evidence suggests that allosteric modulators have adverse pharmacological effects when bound to the monomeric, compared to the dimeric form of these receptors (El Moustaine et al., 2012). Investigating the neurodevelopmental expression of dimeric and monomeric mGluR1 and mGluR5 may highlight possible implications for novel therapeutics at critical neurodevelopmental periods.

Methods: Pregnant Sprague-Dawley rats were obtained at gestational day 14. Offspring were euthanised on postnatal day (PN) 12, 35 and 96 (n=6/group) coinciding with juvenile, adolescent and adult time points. Immunoblots were performed on prefrontal cortex (PFC) and hippocampal tissue under non-reducing conditions to measure dimeric and monomeric mGluR1 and mGluR5 proteins.

Results: Dimeric mGluR1 and mGluR5 was expressed in higher abundance than their monomeric forms. mGluR1 dimeric expression was lowest at PN12 in both the PFC and hippocampus; where it displayed an increase with age. Whilst monomeric mGluR1 expression was considerably lower, it showed a similar trend in the PFC, however, its expression remained constant in the hippocampus. In contrast, dimeric mGluR5 protein expression in the PFC peaked at PN12 and decreased throughout the neurodevelopmental time-points, however its expression in the hippocampus remained constant throughout. Interestingly, in both regions mGluR5 monomer was highly expressed at PN12, almost equal to dimeric expression and then declined to the lowest limits of detection at later time-points.

Conclusion: The monomeric form of mGluR5 is relatively abundant during early post-natal development. Considering positive allosteric modulators exert an unregulated agonist effect when bound to the monomeric form of mGluRs, administration of these compounds during such a critical neurodevelopmental period, may cause seizures and neurotoxic effects, posing possible consequences for novel mGluR5 therapeutics.

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PM492

Schizophrenia patient-derived induced pluripotent stem cells exhibit changes in neurogenic and gliogeniccompetences

Manabu Toyoshima1, Wado Akamatsu1, Yohei Okada2,3, Hideyuki Okano4 and Takeo Yoshikawa4

1 Laboratory of Molecular Psychiatry, RIKEN Brain Science Institute, Saitama, Japan; 2 Department of Physiology, Keio University School of Medicine, Tokyo, Japan; 3 Center for Genomic and Regenerative Medicine, Juntendo University School of Medicine, Tokyo, Japan; 4 Department of Neurology, School of Medicine, Aichi Medical University, Aichi, Japan;

Abstract

To obtain insight into abnormalities in neurodevelopmental trajectories of schizophrenia, analyses of patient-derived human induced pluripotent stem cells (hiPSCs) should be informative. Given the extreme complexity and heterogeneity of genomic architecture underlying ‘general schizophrenia’, analyses of schizophrenia patients with the 22q11.2 deletion could be beneficial because the deletion is one of the highest risk factors. We established hiPSCs from two schizophrenia patients with the 22q11.2 deletion and three controls. Neurosphere size, neural differentiation efficiency, neurite outgrowth and neurogenic-to-gliogenic competence ratio were significantly reduced in the patient-derived cells. As an underlying mechanism, we focused on the role of Dgcr8, a key gene for microRNA (miRNA) processing and mapped in the deleted region. In mice, Dgcr8 hetero-knockout is known to show a similar phenotype of reduced neureplosphere size. miRNA profiling detected reduced expression levels of miRNAs belonging to miR-17/92 cluster and miR-106a/b in the patient-derived neurospheres. Those miRNAs are reported to target p38α, and conformingly the levels of p38α were up-regulated in the patient-derived cells. p38α is known to drive gliogenic differentiation. Inhibition of p38 activity by SB203580 in patient-derived neurospheres partially restored neurogenic competence. Furthermore, we confirmed an elevated expression of GFAP, a gliogenic (astrocyte) marker, in postmortem brains from schizophrenia patients. These results suggest that a dysregulated balance of neurogenic and gliogenic competences may underlie ‘general’ schizophrenia.

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Interactions of tardive dyskinesia with cognitive function in patients with schizophrenia: worsening of working memory with clozapine treatment

Soo In Kim1, Myung Ae Lee2, Karuna Jayathilaka1 and Herbert Y. Meltzer3

1 a. Department of Psychiatry, School of Medicine, Ewha Womans University, Seoul, South Korea; b. Department of Psychiatry, School of Medicine, Vanderbilt University, Nashville, TN; c. Tennessee Valley VA Healthcare System, Nashville Campus, Nashville, TN; d. Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL.

Abstract

Objective: There is evidence that tardive dyskinesia (TD) is associated with greater cognitive impairment. Patients with schizophrenia (SCZ) with TD (SCZ-TD+) was reported to improve less than SCZ without TD (SCZ-TD¯) on some cognitive tests during treatment with antipsychotic drugs (APDs) other than clozapine (Caroff et al., J Clin Psychiatry, 2011). Clozapine improves some cognitive functions, especially, verbal fluency (VF). It improves working memory (WM) in the subset of patients who have higher N-desmethylclozapine (NDMC) clozapine plasma ratio (Meltzer, Am J Psychiatry, 2015). However, overall, it worsens WM (Hagger et al., Biol Psychiatry, 1993). We have, now, examined the impact of TD on cognition after 6 wks of clozapine treatment, with special attention to WM and VF, along with assessments of the impact of clozapine and NDMC levels, and their ratio on cognition in a subsample.

Methods: One hundred seventeen patients (24 SCZ-TD+) were administrated a comprehensive cognitive, as well as psychopathology, assessments, at baseline and after 6 wks of clozapine

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Results: At baseline, SCZ-TD showed significantly lower scores on the Controlled Word Association Test (CWAT), a phonemic VF test, compared to SCZ-TD (p<0.003). No other cognitive test differed significantly between groups. At 6 wk, clozapine significantly improved CWAT (p<0.02) and worsened Consonant Trigram Test (CTT) (p<0.03), a verbal WM test, in both groups. In addition, their changes at 6 wk were negatively correlated (p<0.03). TD’ was associated with significantly greater worsening of performance on the CTT (p<0.05). Plasma drug levels and their ratio were not different between groups, and was not associated with CTT or CWAT at 6 wk. TD status did not affect psychopathology at baseline or at 6 wk.

Conclusions: These data provide new evidence that dorsal striatal deficits, which underlie TD, may be related to cognitive impairment mediated via frontostriatal network in SCZ-TD’. They reinforce the need for less use of typical APDs, which has an increased risk for TD, and the need to take TD status into account in assessing cognition in SCZ and related disorders.

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Conflicts of interest: HYM-grant support or consultant to Lundbeck, Sunovion, Teva, Allergan, Dainippon Sumitomo, Eli Lilly, Janssen, ACADIA, Allergan, Dainippon Sumitomo, Eli Lilly, Janssen, Lundbeck, Sunovion, Teva (Auspex). Other authors do not have conflicts of interest to report.

PM494
So-called D-neuron (trace amine neuron) is a new clue for schizophrenia research: From therapeutic direction
Keiko Ikimoto1, Michel Jouvet2, Kunio Kitahama3
1Iwaki Kyoritsu General Hospital, Japan, 2Claude Bernard Uni, France

Abstract
So-called D-neuron (trace amine (TA) neuron) is the ligand neuron of trace amine-associated receptor, type 1 (TAAR1). Reduced stimulation of TAAR1 on dopamine (DA) neurons in the midbrain ventral tegmental area (VTA) has been revealed to increase firing frequency of VTA DA neurons. A Patent Cooperation Treaty (PCT)-required histochemical methods (K. Ikemoto) were used to specify subgroups of D-neurons in the human brain (Ikemoto et al. 1997, 2016 (in press)), and to show D-neuron decrease in the nucleus accumbens (Acc) (D16, subgroup of D-neurons) of postmortem brains with schizophrenia (Ikemoto et al. 2003). The human D-neuron system is found to be far developed in the forebrain in comparison with that of other species, including non-human primates (Kitahama et al.2009). TA decrease caused by D-neuron reduction, and consequent TAAR1 stimulation decrease on terminals of midbrain VTA DA neurons leads to mesolimbic DA hyperactivity. Neural stem cell (NSC) dysfunction in the subventricular zone of lateral ventricle, which overlaps with the Acc, is supposed to be the cause of D-neuron reduction of schizophrenia. The rational is that the “D-cell hypothesis (TA hypothesis)” (Ikemoto 2012) is essential hypothesis to link DA hypothesis (Hokfelt et al, 1974) with NSC dysfunction hypothesis (Reif et al. 2006). From a therapeutic direction, (1) TAAR1 agonists or TAAR1 partial agonists (Revel et al. 2013), (2) DA D2 antagonists, and (3) neurotropic substances (e.g., brain-derived neurotrophic factor (BDNF), lithium, anticonvulsants, and antidepressants) have potential to normalize mesolimbic DA hyperactivity. Intrasal administration of these neuroactive substances and/or their precursors to reach the neuroleptic acting site, such as the subventricular-accumbal region, by using nanotechnology, is a possible prospective therapeutic strategy, which is devoid of gastrointestinal side effects.

PM495
Neuropathology and functional analysis of schizophrenia associated variant in the MIR137 locus
Murray Cairns, Heath Cairns, Adam Carroll, Simonne Sherwin
University of Newcastle, Australia

Abstract
Small non-coding microRNA (miRNA) coordinate mRNA translation in the brain, and their dysregulation has significant consequences in neurodevelopmental disorders. This hypothesis is supported by strong genetic evidence at the genome-wide associated variant in MIR137 (rs1625579) in recent PGC mega analysis of schizophrenia. We used a TaqMan genotyping and expression strategy to investigate the allelic expression (rs2660304) in post-mortem DLPCF from subjects with schizophrenia and controls with no history of psychiatric disorder (n=74). While no significant difference was observed in the expression of miR-137 in postmortem DLPCF between the controls and schizophrenia, we found that mature miR-137 expression was significantly reduced in the samples homozygous for the risk allele compared to those homozygous for the alternative. Expression in the heterozygotes was not significantly different to either of the homozygotes, however, when we examined the allelic imbalance by differentiating pri-miR-137 expression at each allele (rs2660304), the risk allele was significantly lower compared to the alternative. Functional consequences of dysregulated miR-137 in neurons was then examined human SH-SY5Y neuroblasts electroporated synthetic miR-137 and its antisense antagonist using gene expression profiling. While expression of miR-137 produced relatively few changes in target gene expression the repression of miR-137 in these cells produced changes in a large number of target genes, many of which have also been associated with schizophrenia. These genes were also enriched in several pathways believed to be involved in the neuropathology of the disorder including, axon guidance, glucocorticoid receptor signalling, ErbB signalling, dopamine-DARPP32 feedback in camp signalling, and mTOR signalling. This suggests that the risk variant in MIR137 is an eQTL and results in haploinsufficiency in carriers causing dysfunction in several pathways relevant to schizophrenia.

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How delusion is formed?
Hee Jun Kim, M.D., Jong Suk Park, M.D., Ung Gu Kang
1Department of Psychiatry, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110–744, Republic of Korea b Department of Psychiatry and Behavioral Science, Seoul National