Sub Topic(by disorder): [Attention deficit / Dimentia / Schizophrenia / (others)]
Sub Topic(by methodology): [Neurophysiology / Computational Neuroscience / (others)]

PM509

Homeostatic synaptic plasticity of parvalbumin-positive inhibitory interneurons confers cognitive dysfunction in medial prefrontal cortex.

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Abstract

NMDA receptor (NMDAR) hypofunction in parvalbumin-positive inhibitory interneurons (PV-IN) may underlie the pathogenesis of psychiatric diseases such as autism and schizophrenia by excitation-inhibition (E/I) imbalance. However, cellular mechanism of cognitive dysfunction by NMDAR hypofunction in PV-IN is still unclear. It remains uncertain how chronic NMDAR hypofunction in PV-IN leads to E/I imbalance at basal as well as evoked synaptic strength. Here, we applied not only *in vitro* system with primary cortical culture pre-treated with the NMDAR antagonist, mk-801 but also *in vivo* mouse model with systemically repeated injection of mk-801 showing several cognitive dysfunctions including hyperlocomotion, impaired working memory, social deficit, and disrupted paired-pulse inhibition (PPI). In *in vitro* primary cortical culture system and medial prefrontal cortex (mPFC) in our *in vivo* mouse model, chronic NMDAR hypofunction in PV-INs induced AMPA receptor (AMPAR) downregulation, while NMDAR and AMPAR in pyramidal neurons (PY) were not affected. Moreover, alteration of synaptic strength in PV-IN is highly correlated with mPFC dependent cognitive function, working memory. The reduced synaptic strength of PV-IN caused disinhibition onto PY and increased E/I ratio, resulting in hyper-excitation in mPFC. This also disturbed synaptic plasticity of PY in mPFC. Reduced AMPAR strength in PV-IN was recovered by microinjection of PKA activator, forskolin into mPFC, giving rise to improved working memory and PPI. Together, these results indicate that chronic NMDAR hypofunction in PV-IN is associated with downregulation of AMPAR through PKA inactivation, which leads to E/I imbalance in mPFC by disinhibition onto PY, conferring psychiatric symptoms.

Key words: NMDAR hypofunction, Homeostatic synaptic plasticity, E/I balance, Parvalbumin-positive inhibitory interneuron, Medial prefrontal cortex, Psychiatric symptoms

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Temporal relationship of mismatch negativity multiple generators in patients with schizophrenia and subjects at clinical high risk for psychosis

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Abstract

It has been suggested that Mismatch negativity (MMN) generators lie in temporal and frontal cortices and that these generators show separate time courses in normal healthy subjects. However, little is known about the temporal association of MMN multiple generators in schizophrenia, although aberrant fronto-temporal connectivity is emerging issue in the pathophysiology of schizophrenia. The aim of this study is to investigate the temporal relationship of MMN multiple generators, which may reflect aberrant fronto-temporal functional connectivity in schizophrenia.

The present study assessed duration-deviant MMN using high density electroencephalography during passive oddball task in 29 patients with schizophrenia, 40 subjects at clinical high risk (CHR) for psychosis, and 47 healthy control (HC) subjects. Individual realistic head model, incorporating anatomical data from each individual's magnetic resonance image, was constructed. Minimum L2 norm algorithm was used to generate MMN current source density (CSD) model of MMN response over time. The strength of CSD and its time course were compared across groups.

Patients with schizophrenia and CHR subjects showed reduced MMN CSD strength compared to HC subjects in both frontal and temporal cortices. We also found significant time difference between temporal and frontal MMN generators in both CHR and HC groups, indicating that frontal MMN generators were activated later than temporal MMN generators. However, normal sequential generator activity was not found in patients with schizophrenia, with significantly increased variability of generator time behavior. In conclusion, schizophrenia patients showed both reduced and aberrant generator activity, while CHR subjects only showed reduced generator activity with relatively normal time behavior. Our findings suggest that aberrant fronto-temporal connectivity may emerge after the frank psychotic episode and may demarcate boundary between overt and early psychosis state.

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Determinants of Caregiver Burden in Family Carers of Asian Patients with Schizophrenia treated with Paliperidone Palmitate 3-monthly injectable

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Abstract

Objective: Caregiving-associated burden in schizophrenia and its assessment require cross-cultural validation to identify risk groups and family functioning. In a post-hoc analysis, data of two double-blind, phase-3 studies were pooled to assess the level of perceived burden among carers of Asian patients with schizophrenia treated with paliperidone palmitate 3-month (PP3M) or 1-month long-acting injectable (LAI).

Methods: Carers (family member/friend in contact with patient for ≥1hour/week) rated their burden of patient's illness on 0–5 scale using 31-item Involvement Evaluation Questionnaire (IEQ), which contains four subscales (domains): tension (9-items), worrying (6-items), supervision (6-items) and urging (8-items).

Results: Among 412 carers (52% parents) of Asian patients with schizophrenia, >59% reported a burden of caregiving to patients with schizophrenia for ≥32 hours/week. Carer (n=171) burden reduced significantly (mean improvement [SD]: 6.8 [18.48], p-value<0.001) from baseline (mean [SD]: 30.8 [17.10]) to study end (24.0 [17.14]), predominantly relieving the burden associated with worrying (2.6 points) and urging (2.7 points) domains. IEQ scores improved for patients without relapse (mean [SD]