Abstract

Object: This study investigated the relationship between erythrocyte membrane fatty acid (FA) levels and the severity of symptoms of individuals at ultra-high risk(UHR) for psychosis.

Methods: The study sample consisted of 80 neuroleptic-naive UHR patients. Associations between baseline erythrocyte membrane FA levels, measured by gas chromatography, and scores on the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning Scale, and the Montgomery–Asberg Depression Rating Scale (MADRS) were investigated. After correlation analysis in all participants, subjects were divided into three groups according to the predominance of positive or negative symptoms based on PANSS subscale scores; membrane FA levels in the three groups were then compared.

Results: PANSS negative symptom scores were negatively correlated with two saturated FAs (myristic and margaric acids), one ω-9 monounsaturated FA (MUFA; nervonic acid), and one ω-3 polyunsaturated FA(PUFAs; docosapentaenoic acid). Negative symptom scores were positively correlated with two ω-9 MUFAs(eicosenoic and erucic acids) and two ω-6 PUFAs (γ-linoleic and docosahexaenoic acids). PANSS positive symptom scores were correlated only with nervonic acid. No associations were observed between FAs and MADRS scores. In subjects with dominant negative symptoms, the sum of the ω-9 MUFAs and the ω-6:ω-3 FA ratio were both significantly higher than in those with dominant positive symptoms, whereas the sum of ω-3 PUFAs was significantly lower.

Conclusions: Abnormalities in FA metabolism may contribute to the neurobiology of psychopathology in UHR individuals. In particular, membrane FA alterations may play a role in negative symptoms, which are primary psychopathological manifestations of schizophrenia-related disability.

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Presynaptic protein Piccolo knockdown in the prefrontal cortex induces cognitive and emotional impairment in mice.

Yoshiaki Miyamoto1, Ryo Inagaki1, Keiji Sato1, Shin-ichi Muramatsu2, Toshitaka Nabeshima3, Kyosuke Uno1, Atsumi Nitta1

1Department of Pharmaceutical Therapy and Neuropharmacology, Faculty of Pharmaceutical Sciences, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, JAPAN. 2Division of Neurology, Department of Medicine, Jichi Medical University, Shimotsuke 329–0498, JAPAN. 3Nabeshima Laboratory, Meijo University, Nagoya 468–8503, JAPAN.

Abstract

Piccolo, a protein of the cytomatrix at the active zone, is involved in the exocytosis and endocytosis of the synaptic vesicles at the presynaptic bouton. It is reported recently that the expression level of Piccolo-encoded PCLO mRNA and Piccolo itself changed in the brain of the bipolar disorder and schizophrenia patient. In the present study, therefore, to clarify the neurological function of Piccolo in the development of mental disorders, we generated Piccolo deficient animal by bilaterally microinjecting the adeno-associated virus vector containing PCLO miRNA into the prefrontal cortex of the mouse.

In the electrophysiological analysis, the Piccolo knockdown mice showed augmented the paired-pulse facilitation and long-term potentiation in the prefrontal cortex. In the same prefrontal cortex, the phosphorylation level of synaptic vesicle binding protein Synapsin significantly decreased in the Piccolo knockdown mice, but the remarkable abnormalities were not observed on the shape of dendrite and spine and on the expression level of Synaptophysin, NMDAR1 and PSD-95 in the mice. In the behavioral analysis, the Piccolo knockdown mice showed decreased cognitive dysfunction including object recognition, spatial learning and working memory. Furthermore, the locomotor activity in the novel environment increased in the Piccolo knockdown mice, and its hyperlocomotion was improved by the treatment with atypical antipsychotic drug risperidone. Similarly, the impaired prepulse inhibition of the acoustic startle responses in the Piccolo knockdown mice was ameliorated by risperidone.

These results suggest that Piccolo in the prefrontal cortex regulates the release of the neurotransmitter from the presynaptic membrane, and it consequently plays a functional role in the synaptic plasticity, cognitive memory and emotional activity. Furthermore, our observations indicate that the mouse with Piccolo deficient in the prefrontal cortex is useful animal model for the mental disorders such as the manic symptom of bipolar disorder or the positive symptom of schizophrenia.

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Activation of Galphaq proteins coupled with dopamine D1-like receptor and alpha1-adrenoceptor in rat brain membranes

Yuji Odagaki, Masakazu Kinoshita, Toshio Ota

Saitama Medical University, Japan

Abstract

Objectives: Previously, we reported 5-HT2A receptor- and M1 muscarinic acetylcholine receptor (mAChR)-mediated Gq activation in rat brain membranes (Eur J Pharmacol 726: 109–115, 2014). In this paper, it was noticed that Gq proteins were also activated by dopamine and (-)-epinephrine, although these effects were much lower than that elicited by 5-HT or carbachol. In the present study, activation of Gq coupled to dopaminergic and adrenergic receptor was pharmacologically characterized in rat brain membranes.

Methods: Receptor-mediated activation of Gq in rat brain membranes was assessed by guanosine-5’-O-(3-hydroxymethyl) triphosphate ([35S]GTP·S) binding/immunoprecipitation assay (Eur J Pharmacol 726: 109–115, 2014), with minor modifications.

Results: In cerebral cortical membranes, dopamine and (-)-epinephrine stimulated specific [35S]GTP·S binding to Gq in a concentration-dependent manner, with EC50 values of 65 and 0.46 μM, to the maximal percent increase over basal binding of 99 and 70 %, respectively. The responses in hippocampus and striatum were lower than those in cerebral cortex for either compound. Pharmacological characterization using a series of dopaminergic and adrenergic compounds indicated that dopamine- and (-)-epinephrine-stimulated specific [35S]GTP·S binding to Gq was mediated through dopamine D1-like receptor and α1-adrenoceptor, respectively. In these assay systems, however, some compounds behaved against all expectations. For instance, (R)-(−)-SCH23390 and SKF83566, both of which were usually regarded as dopamine D1-like receptor antagonists, exhibited agonistic effects. The α1-adrenoceptor agonist (R)-(−)-phenylephrine did not stimulate the specific [35S]GTP·S binding to Gq. Although oxymetazoline acted as an agonist, this effect appeared to be mediated by 5-HT2α receptor, but not by adrenergic receptors.