Suppressing leukocyte Kv1.3-channels by commonly used drugs: A novel therapeutic target for schizophrenia?

Yasuhiro Sato, Ryo Kuwana, Itsuro Kazama*

Miyagi University, School of Nursing, Taiwa-cho, Miyagi, Japan.

SUMMARY Recent studies revealed the involvement of "chronic inflammation" in the pathogenesis of schizophrenia. In schizophrenia and some neurodegenerative disorders that are caused by inflammation, T-lymphocytes and macrophages were hyperactivated or proliferated in the central nervous system, being accompanied by the overexpression of delayed rectifier K⁺-channels (Kv1.3) within the cells. In our previous basic studies, in addition to nonsteroidal anti-inflammatory drugs (NSAIDs) and statins, antibiotics (clarithromycin, chloroquine), anti-hypertensive drugs (nifedipine, bendipine, diltiazem, verapamil) and anti-allergic drugs (cetirizine, fexofenadine, azelastine, terfenadine) strongly suppressed the Kv1.3-channel activity and pro-inflammatory cytokine production from lymphocytes. Given such pharmacological properties of these commonly used drugs, they may be useful in the treatment of schizophrenia, in which the enhanced cellular immunity and the subsequent release of excessive cytokines are responsible for the pathogenesis.

Keywords Schizophrenia, chronic inflammation, lymphocyte, Kv1.3-channels, nonsteroidal anti-inflammatory drugs (NSAIDs), statins

Schizophrenia is a chronic brain disorder which affects approximately 0.7 to 1.1% of world population (1). It is characterized by continuous or relapsing episodes of psychosis, presenting with symptoms such as hallucinations, delusions, paranoia and disorganized thinking. Besides the contribution of genetic or environmental factors, studies revealed that abnormalities of neurotransmitters, such as dopamine and glutamate, play major roles in the pathogenesis of schizophrenia (1). Therefore, targeting hyperactivated dopamine system, antipsychotics have commonly been used in the treatment of schizophrenia, since they persistently block postsynaptic dopamine 2 (D2) receptors (1). However, both typical and atypical antipsychotics can cause serious side effects, including movement disorders, metabolic syndrome, cardiac arrhythmia and sexual dysfunction (2). Such side effects frequently cause the drug discontinuation in the schizophrenia patients and the subsequent relapse of psychotic symptoms.

Recent advances in molecular pathology have additionally revealed the involvement of "chronic inflammation" in the pathogenesis of schizophrenia (3,4). In patients with schizophrenia, besides the inflammatory markers, such as serum C-reactive protein (CRP) levels and the neutrophil-lymphocyte ratio (5,6), pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α), were actually increased in both peripheral blood and the cerebral spinal fluid (7). These cytokines directly or indirectly contribute to the psychopathology of schizophrenia by disturbing the brain connectivity, neurodevelopment, neurogenesis and the neurotransmitter function. Microglia are the brain-resident macrophages that produce pro-inflammatory cytokines within the central nervous system (3,4). In patients with schizophrenia, in addition to microglia, T-lymphocytes, which also produce pro-inflammatory cytokines (8), were activated or proliferated in both peripheral blood and the central nervous system (3,9,10). These findings strongly suggest the involvement of enhanced cellular immunity in the pathogenesis of schizophrenia.

T-lymphocytes and macrophages predominantly express delayed rectifier K⁺-channels (Kv1.3) in their plasma membranes (8). These channels play crucial roles in the activation and proliferation of these leukocytes, which consequently stimulates the cellular immunity (8,11). Using animal models with advanced-stage chronic kidney disease (CKD), we previously revealed that both T-lymphocytes and macrophages were markedly increased and the cytokine levels, such as IL-2 and TNF-α, were significantly elevated within the fibrotic kidneys (8,12). In these leukocytes, Kv1.3-channels were
over-expressed and the pharmacological blockade of the channels actually ameliorated the disease progression. Therefore, the Kv1.3-channels were thought to be responsible for the overactivation of cellular immunity and the subsequent progression of renal fibrosis (8,12). Recently, in addition to chronic diseases, including CKD, chronic obstructive pulmonary disease and inflammatory bowel disease (8), some neurodegenerative disorders, such as multiple sclerosis, Alzheimer's disease and Parkinson's disease, are also considered to be caused by inflammation (13). In such diseases, T-lymphocytes and macrophages were hyperactivated or proliferated in the central nervous system, being accompanied by the overexpression of Kv1.3-channels within the cells (13).

In the treatment of schizophrenia, recent clinical studies have additionally revealed the therapeutic efficacy of anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, anti-hypertensives and anti-allergic drugs, which inhibit Kv1.3-channels, suppress the enhanced cellular immunity and the subsequent release of excessive cytokines.

In addition to NSAIDs and statins, some of the antibiotics, anti-hypertensive drugs and anti-allergic drugs strongly suppressed the Kv1.3-channel activity and pro-inflammatory cytokine production from lymphocytes. Given such pharmacological properties of these commonly used drugs, they may be useful in the treatment of schizophrenia, in which the enhanced cellular immunity and the subsequent release of excessive cytokines are responsible for the pathogenesis.

Conclusion

In our series of patch-clamp studies thus far, we further demonstrated the inhibitory properties of antibiotics (clarithromycin, chloroquine), anti-hypertensive drugs (nifedipine, benidipine, diltiazem, verapamil) and anti-allergic drugs (cetirizine, fexofenadine, azelastine, terfenadine) on lymphocytes Kv1.3-channels (8,18,19). Considering such pharmacological properties of these commonly used drugs, they would also be useful in the treatment of schizophrenia, since the channel inhibition suppresses the activity of brain lymphocytes or macrophages and thus represses their cytokine production (Figure 1). Compared to the highly selective Kv1.3-channel inhibitors that were originally derived from scorpion venom or sea anemone peptide toxins (20), the drugs, such as NSAIDs, statins, antibiotics, anti-hypertensive drugs and anti-allergic drugs, could be used more harmlessly, because they have commonly been prescribed in a general clinical practice for longer periods of time.

Funding: This work was supported by the Salt Science Research Foundation, No. 2218 to IK.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. Lancet. 2022; 399:473-486.
2. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. World Psychiatry. 2018; 17:341-356.
3. Muller N. Inflammation in schizophrenia: Pathogenetic aspects and therapeutic considerations. Schizophr Bull. 2018; 44:973-982.
4. Fond G, Lancon C, Korchia T, Auquier P, Boyer L. The role of inflammation in the treatment of schizophrenia. Front Psychiatry. 2020; 11:160.
5. Faugere M, Micoulaud-Franchi JA, Alessandrini M, Richieri R, Faget-Agius C, Auquier P, Lancon C, Boyer L. Quality of life is associated with chronic inflammation in schizophrenia: a cross-sectional study. Sci Rep. 2015; 5:10793.
6. Semiz M, Yildirim O, Canan F, Demir S, Hasbek E,
Tuman TC, Kayka N, Tosun M. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatr Danub. 2014; 26:220-225.
7. Miller BJ, Goldsmith DR. Evaluating the hypothesis that schizophrenia is an inflammatory disorder. Focus (Am Psychiatr Publ). 2020; 18:391-401.
8. Kazama I. Physiological significance of delayed rectifier K+ channels (Kv1.3) expressed in T lymphocytes and their pathological significance in chronic kidney disease. J Physiol Sci. 2015; 65:25-35.
9. Muller N, Hofschuster E, Ackenheil M, Eckstein R. T-cells and psychopathology in schizophrenia: relationship to the outcome of neuroleptic therapy. Acta Psychiatr Scand. 1993; 87:66-71.
10. Schlaaff K, Dobrowolny H, Frodl T, Mawrin C, Gos T, Steiner J, Bogerts B. Increased densities of T and B lymphocytes indicate neuroinflammation in subgroups of schizophrenia and mood disorder patients. Brain Behav Immun. 2020; 88:497-506.
11. Kazama I, Senzaki M. Does immunosuppressive property of non-steroidal anti-inflammatory drugs (NSAIDs) reduce COVID-19 vaccine-induced systemic side effects? Drug Discov Ther. 2021; 15:278-280.
12. Kazama I, Baba A, Matsubara M, Endo Y, Toyama H, Ejima Y. Benidipine suppresses in situ proliferation of leukocytes and slows the progression of renal fibrosis in rat kidneys with advanced chronic renal failure. Nephron Experimental nephrology. 2014; 128:67-79.
13. Wang X, Li G, Guo J, Zhang Z, Zhang S, Zhu Y, Cheng J, Yu L, Ji Y, Tao J. Kv1.3 Channel as a key therapeutic target for neuroinflammatory diseases: State of the art and beyond. Front Neurosci. 2019; 13:1393.
14. Hong J, Bang M. Anti-inflammatory strategies for schizophrenia: A review of evidence for therapeutic applications and drug repurposing. Clin Psychopharmacol Neurosci. 2020; 18:10-24.
15. Cakici N, van Beveren NJM, Judge-Hundal G, Koola MM, Sommer IEC. An update on the efficacy of anti-inflammatory agents for patients with schizophrenia: a meta-analysis. Psychol Med. 2019; 49:2307-2319.
16. Kazama I, Maruyama Y, Murata Y. Suppressive effects of nonsteroidal anti-inflammatory drugs diclofenac sodium, salicylate and indomethacin on delayed rectifier K+ channel currents in murine thymocytes. Immunopharmacol Immunotoxicol. 2012; 34:874-878.
17. Kazama I, Baba A, Maruyama Y. HMG-CoA reductase inhibitors pravastatin, lovastatin and simvastatin suppress delayed rectifier K+ channel currents in murine thymocytes. Pharmacol Rep. 2014; 66:712-717.
18. Kazama I, Tamada T, Tachi M. Usefulness of targeting lymphocyte Kv1.3-channels in the treatment of respiratory diseases. Inflamm Res. 2015; 64:753-765.
19. Baba A, Tachi M, Maruyama Y, Kazama I. Suppressive effects of diltiazem and verapamil on delayed rectifier K+ channel currents in murine thymocytes. Pharmacol Rep. 2015; 67:959-964.
20. Han S, Yi H, Yin SJ, Chen ZY, Liu H, Cao ZJ, Wu YL, Li WX. Structural basis of a potent peptide inhibitor designed for Kv1.3 channel, a therapeutic target of autoimmune disease. J Biol Chem. 2008; 283:19058-19065.

Received April 6, 2022; Revised April 17, 2022; Accepted April 18, 2022.

*Address correspondence to:
Itsuro Kazama, School of Nursing, Miyagi University, 1-1 Gakuen, Taiwa-cho, Kurokawa-gun, Miyagi 981-3298, Japan.
E-mail: kazamai@myu.ac.jp

Released online in J-STAGE as advance publication April 21, 2022.