Communication

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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, benidipine, 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

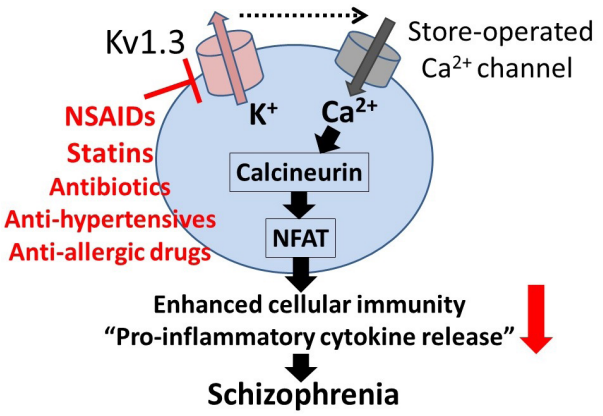

Figure 1. Roles of Kv1.3-channels in the activation pathway of T-lymphocytes or brain macrophages (microglia) and as the targets of commonly used drugs for schizophrenia. Kv1.3-channels promote calcium influx and trigger the proliferation and activation of T-lymphocytes or brain macrophages (microglia). The increased cytosolic calcium concentration stimulates the phosphatase calcineurin, which de-phosphorylates the nuclear factor of activated T cells (NFAT), causing its accumulation in the nucleus and binding to the promoter region of cytokine-encoding genes. Nonsteroidal anti-inflammatory drugs (NSAIDs), statins, antibiotics, anti-hypertensives and anti-allergic drugs, which inhibit Kv1.3-channels, suppress the enhanced cellular immunity and the subsequent release of excessive cytokines.

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 and anti-cholesterol drugs (statins) (*14,15*). Despite the lack of pharmacological evidence, these agents actually lowered the serum CRP levels in schizophrenia patients and suppressed the release of pro-inflammatory cytokines in the brain (*15*). According to our previous patch-clamp studies using murine thymocytes, both NSAIDs, such as indomethacin, diclofenac and salicylate, and statins, such as pravastatin, lovastatin and simvastatin, strongly suppressed the activity of lymphocyte Kv1.3-channels and thus reduced the production of pro-inflammatory cytokines (*16,17*). These findings provide an additional pharmacological mechanism by which NSAIDs and statins were effective for schizophrenia, where the enhanced cellular immunity and the subsequent release of excessive cytokines were responsible for the pathogenesis (Figure 1).

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.

Conclusion

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

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**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

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