Does immunosuppressive property of non-steroidal anti-inflammatory drugs (NSAIDs) reduce COVID-19 vaccine-induced systemic side effects?

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SUMMARY To help stop the coronavirus disease 2019 (COVID-19) pandemic, vaccines are currently the most critical tool. However, the COVID-19 mRNA vaccines frequently cause systemic side effects shortly after the injection, such as fever, headache and generalized fatigue. In our survey, after receiving the second dose of the COVID-19 vaccine, 80% developed fever, 62% headache and 69% generalized fatigue. Among people who required antipyretics, the average durations of fever and headache were significantly shorter in those who took non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, loxoprofen and ibuprofen, than those who took acetaminophen. In our patch-clamp studies, NSAIDs effectively suppressed the delayed rectifier K⁺-channel (Kv1.3) currents in T-lymphocytes and thus exerted immunosuppressive effects. Because of this pharmacological property, the use of NSAIDs should be more effective in reducing the vaccine-induced systemic side effects that are caused primarily by the enhanced cellular immunity.

Keywords Coronavirus disease 2019 (COVID-19), vaccine, side effects, non-steroidal anti-inflammatory drugs (NSAIDs)
arthritis (9). In our previous case reports, NSAIDs were actually effective in reducing systemic symptoms triggered by the enhanced autoimmunity (10,11). Concerning the mechanisms by which NSAIDs exert this immunosuppressive property, NSAIDs inhibit the migration of leukocytes or directly suppress their cytokine production, either cyclooxygenase (COX) -dependently or -independently (12,13). Since the enhanced cellular immunity was the primary pathogenesis of the vaccine-induced side effects, the immunosuppressive effect of NSAIDs was thought to be responsible for the more rapid reduction of fever, headache and generalized fatigue in our survey (Figure 1).

In our patch-clamp studies, we have revealed that NSAIDs, such as aspirin, indomethacin and diclofenac, functionally inhibited delayed rectifier K+ -channels (Kv1.3) expressed in T-lymphocytes, and thus suppressed the activity of the cells (14) (Figure 2). Since the channels are highly expressed in T-lymphocytes (15), and since selective blockade of the channels actually repressed the immune response in lymphocytes (16), this mechanism was thought to be largely responsible for the immunosuppressive property of NSAIDs (Figure 2). Concerning this pharmacological property, besides the use of immunosuppressive drugs or corticosteroids, the use of selective Kv1.3-channel inhibitors may also be beneficial. The early administration of these drugs may not only shorten the duration of the vaccine-induced systemic side effects, but also prevent serious complications after the vaccination, such as myocarditis and pericarditis (17). Recently, we have additionally demonstrated in our patch-clamp studies that drugs such as statins (lovastatin, simvastatin), antibiotics (clarithromycin, chloroquine), anti-hypertensive drugs (nifedipine, bendipide, diltiazem, verapamil) and anti-allergic drugs (cetirizine, fexofenadine, azelastine, terfenadine), also strongly suppress the Kv1.3-channel currents in T-lymphocytes (15,18-20). In this context, besides NSAIDs, these drugs may also be potentially effective in reducing vaccine-induced systemic side effects.

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