Brief Communication

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Anti-vasospastic mast cell stabilizers: a novel therapeutic approach to anaphylaxis-induced acute coronary syndrome

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Kounis syndrome is an acute myocardial infarction caused by severe allergic reactions or anaphylaxis following vaccination and other triggers, with the associated release of chemical mediators from mast cells causing coronary artery vasospasm. However, treatment with adrenaline is controversial as it paradoxically aggravates cardiac ischemia. Among the many a_1-adrenergic receptor blockers, calcium channel blockers, endogenous vasodilators, and antioxidants that can ameliorate coronary artery vasospasm are some (e.g., prazosin, verapamil, diltiazem, magnesium and vitamin C) that can also stabilize mast cells. Given their dual pharmacological efficacies, these substances may be valuable treatments for Kounis syndrome following coronavirus disease 2019 and other vaccinations.

Keywords: COVID-19 vaccines; Kounis syndrome; Coronary artery vasospasm; Mast cell stabilizer

Despite decreasing numbers of seriously ill patients, coronavirus disease 2019 (COVID-19) remains a life-threatening disease, particularly for elderly and immunocompromised patients. COVID-19 vaccines significantly prevent individuals from being infected, protect infected people from the onset of symptoms, and can reduce the severity of the illness with high efficacy. However, in addition to common self-limiting side effects such as fever, headache, and generalized fatigue, the vaccines can also cause fatal cardiovascular or cerebrovascular complications, including hypertensive crisis, aortic dissection, acute myocardial infarction, subarachnoid hemorrhage, ischemic or hemorrhagic strokes, and venous thromboembolism [1]. Concerning their pathogenesis, vaccine-induced hypertension, thrombosis, thrombocytopenia, and hyperimmune responses are primarily responsible for these outcomes. However, not all cases are accompanied by increases in serum biomarkers of coagulation or inflammation such as d-dimers or various cytokines.

Kounis syndrome is an acute myocardial infarction caused by severe allergic reactions or anaphylaxis [2]. The first choice treatment for anaphylaxis is an immediate injection of adrenaline. However, the use of adrenaline alone is controversial in the treatment of Kounis syndrome as it can exacerbate coronary artery vasospasm [3], thus aggravating cardiac ischemia [4].

In reports of eight cases of acute myocardial infarction after COVID-19 vaccination,

most patients initially presented with symptoms or signs of anaphylaxis following vaccine administration with subsequent acute myocardial infarction [4,5] and were diagnosed with Kounis syndrome [2]. A large epidemiological study in the U.S. revealed that among 235,420 hospital patients admitted because of allergic or hypersensitivity reactions, 1.1% presented with acute coronary syndrome and were subsequently diagnosed with Kounis syndrome [6]. The development of Kounis syndrome is also associated with the use of antibiotics, nonsteroidal anti-inflammatory drugs, antineoplastic drugs, iodinated contrast media, and vaccines. Foods (eggs, shellfish, fruits, or vegetables), environmental exposure (animal licking, insect bites, metal exposure, or latex contact), and clinical conditions (bronchial asthma, hay fever, or intracoronary stenting) have also been identified as potential triggers [7].

Concerning the pathogenesis of Kounis syndrome, the activation of mast cells is primarily responsible for the allergic reactions and subsequent development of acute coronary syndrome (acute myocardial infarction or angina pectoris) associated with Kounis syndrome (**Fig. 1**), with three recognized variants of the syndrome (type I to III) related to the severity of preexisting coronary atherosclerosis [7]. Upon exposure to allergens, mast cells immediately release chemical mediators such as histamine, leukotrienes, prostaglandins, and platelet-activating factors through an exocytotic process [2,7]. These mediators, which are responsible for the systemic allergic reactions or anaphylaxis also induce coronary artery vasospasm, eventually cause total or subtotal occlusion of the arteries and the development of acute coronary syndrome [2,7] (**Fig. 1**). In COVID-19 vaccine-induced Kounis syndrome, the common ingredient or excipient of the vaccines, such as polyethylene glycol and polysorbate-80, has been shown to stimulate the degranulation of chemical mediators from mast cells, causing the anaphylaxis [8,9].

The treatment of Kounis syndrome is usually difficult, as the allergic reactions must be addressed simultaneously with the cardiac ischemia [7]. For instance, antihistamines such as diphenhydramine and ranitidine are commonly recommended for the initial treatment of the allergic reactions [4,7], but must be used carefully as they may also exert cardiotoxic properties [10]. Further, their bolus administration can precipitate hypotension and compromise coronary artery flow [7], exacerbating cardiac ischemia. Adrenaline, a nonspecific adrenergic receptor agonist, is the drug of choice for emergency treatment of anaphylaxis because it rapidly reverses cardiovascular collapse and ameliorates airway obstruction by stimulating b-adrenergic receptors. Additionally, adrenaline immediately alleviates serious allergic reactions through its mast cell-stabilizing properties [11]. Concerning the mechanism, adrenaline stimulates b_2-adrenergic receptors, suppressing further secretion of chemical mediators from the mast cells. However, because adrenaline also stimulates a-adrenergic receptors in vascular smooth muscle cells [4,7], it can exacerbate coronary artery vasospasm [3]. Additionally, due to anaphylaxis-mediated systemic vasodilation and reduced cardiac output in Kounis syndrome, the cardiac muscles and coronary vessels are prone to hypoperfusion [12] where adrenaline further aggravates cardiac ischemia [4,7].

According to several case reports, drugs and substances such as prazosin, magnesium, and vitamin C are effective for treating Kounis syndrome [6,13,14]. However, little is known about the mechanisms underlying their therapeutic efficacy.

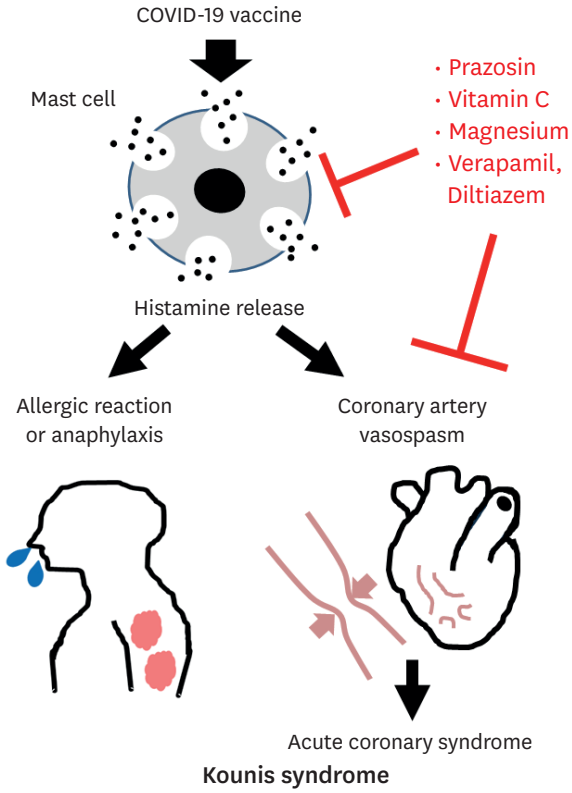

Fig. 1. Mechanisms of COVID-19 vaccine-induced Kounis syndrome and therapeutic efficacies of mast cells stabilizers that can ameliorate coronary artery vasospasm. Mast cells are activated by COVID-19 vaccine administration, releasing secretory granules containing histamine and other components. In addition to severe allergic reactions or anaphylaxis, this results in coronary artery vasospasms, leading to the development of acute coronary syndrome. Mast cell stabilizers that ameliorate coronary artery vasospasm, such as prazosin, vitamin C, magnesium, verapamil, and diltiazem, exert dual therapeutic efficacy against Kounis syndrome.
COVID-19, coronavirus disease 2019.

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In addition to the stimulation of autonomic nerves through a-adrenergic receptors, studies have revealed the involvement of smooth muscle hypercontractility and oxidative stress in the pathogenesis of coronary artery vasospasm [15]. Based on these observations, there is evidence of the therapeutic efficacies of a_1-adrenergic receptor blockers (prazosin), calcium channel blockers (verapamil and diltiazem), endogenous vasodilators (magnesium) and antioxidants (vitamin C) in the treatment of vasospastic angina [15,16].

In contrast, in our series of patch-clamp studies monitoring the changes in whole-cell membrane capacitance (Cm) in mast cells isolated from rat peritoneal cavity, we provided *in vitro* evidence that commonly used drugs (e.g., antihypertensives, antibiotics, and corticosteroids) or daily food components (e.g., vitamins, lemon juice, and lemon peel constituents) also suppress the process of exocytosis [17,18] (**Fig. 2**). This work was based on the observation that increases in Cm reflect the increase in total mast cell surface area resulting from exocytosis (**Fig. 2A**). Conversely, a failure of Cm to increase despite internal stimuli for exocytosis would indicate that the process of exocytosis was inhibited (**Fig. 2B**). In our previous studies, drugs or substances that suppressed increases in Cm inhibited morphological degranulation from mast cells [17,18], suggesting their potency as highly effective mast cell stabilizers. We have further found that prazosin and vitamin C, which ameliorate coronary artery vasospasm [15,16], strongly exert mast cell-stabilizing properties [11,17,18]. Of note, the co-administration of prazosin and adrenaline synergistically enhances the mast cell-stabilizing properties of adrenaline [11], while low-dose vitamin C exerts synergistic effects when combined with other vitamins [17]. Using experimental animal models or isolated cells, previous studies have also revealed the strong potency of magnesium and L-type calcium channel blockers such as verapamil and diltiazem in mast cell stabilization [19,20]. Given such dual pharmacological efficacies (i.e., "anti-vasospastic properties" and "mast cell-stabilizing properties"), these drugs and substances may be useful in the treatment of Kounis syndrome following COVID-19 vaccination (**Fig. 1**), where the use of adrenaline alone may worsen the disease [4,7].

In conclusion, among the a_1-adrenergic receptor blockers, calcium channel blockers, endogenous vasodilators, and antioxidants commonly used to ameliorate coronary artery vasospasm are specific drugs and substances such as prazosin, verapamil, diltiazem, magnesium, and vitamin C that additionally exert mast cell-stabilizing properties. Given such dual pharmacological efficacies, these therapies may be beneficial in the treatment of Kounis syndrome following COVID-19 vaccination. Large-scale clinical studies are needed to adequately evaluate their therapeutic efficacy.

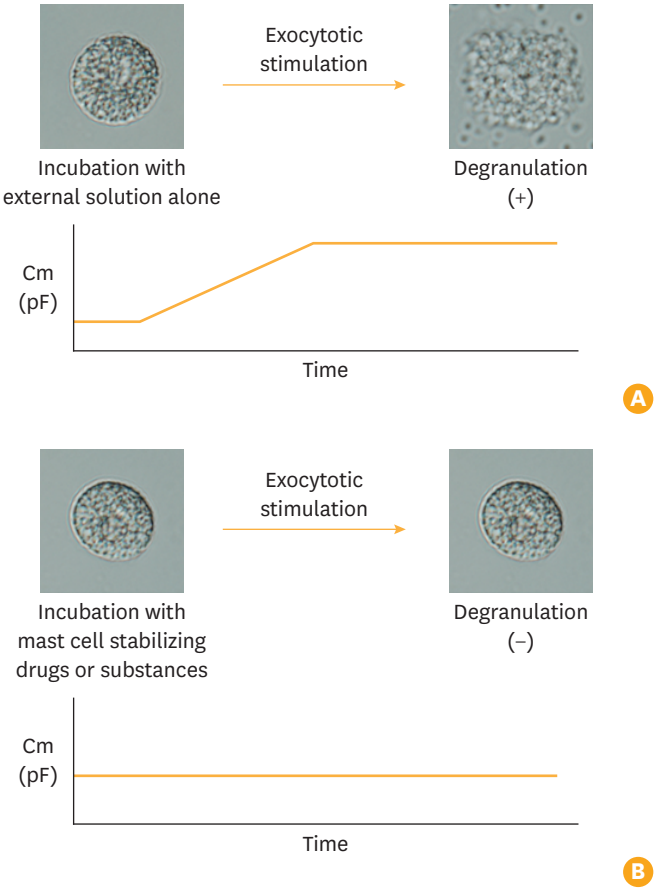

Fig. 2. Electrophysiological evidence for mast cell-stabilizing property. (A) Upon external stimulation for exocytosis, rat peritoneal mast cells show additional wrinkles on their cell surfaces and release secretory granules (degranulation), indicating exocytosis. As a result, Cm gradually increases, representing an increase in total cell surface area. (B) Mast cells were pre-incubated with assorted mast cell stabilizing drugs or substances (mast cell-stabilizers) before exocytosis was induced. This suppressed the increase in Cm and degranulation from the mast cells, demonstrating prophylactic efficacy against anaphylaxis.
Cm, membrane capacitance.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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