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Histamine-Mediated Hypersensitivity Following COVID-19 Vaccination

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ABSTRACT

COVID-19 mRNA vaccines are known to induce histamine-associated hypersensitivity reactions, anywhere between mild urticaria and anaphylaxis, which can be attributed to numerous distinct pathways such as IgE-mediated sensitization to vaccine-derived PEG-lipid components, complement activation-related pseudoallergy (CARPA), activation of MRGPRX2, and cytokine-induced mast cell degranulation. These immediate reactions can therefore be traced back to cytokine release syndrome (CRS) resulting from lipid nanoparticles (LNPs) as well as anaphylaxis due to PEG, both key components of mRNA-LNPs vaccines, with histamine release by mast cells being one of the key drivers of the allergic response. While pharmaceutical interventions such as epinephrine, antihistamines, corticosteroids, and omalizumab are currently the standard treatment modalities for such reactions and will likely remain so, their adverse effects profile, including immunosuppression, hyperglycemia, neuropsychiatric symptoms, and anaphylaxis, among others, necessitates low-risk supportive therapies for high-risk individuals. Functional nutrition has emerged as a popular adjuvant to conventional treatment modalities and is currently being explored in many studies. In fact, certain nutrients have been shown to influence mast cell activity and decrease histamine production as well as allergic mediator release comparably to pharmaceutical options. Quercetin, curcumin, EGCG and essential micronutrients such as vitamin C, vitamin D, zinc, magnesium, and omega-3 all provide beneficial effects through stabilizing mast cells, rebalancing Th1/Th2 responses, decreasing IgE production, inhibiting NF-κB/MAPK signaling, and providing antioxidant support, among other mechanisms. Therefore, a functional nutrition-based approach could serve as a low-risk strategy to reduce COVID-19 vaccine-induced allergic reactions when paired with conventional pharmaceutical care and personalized risk assessment before vaccination.

Keywords: COVID-19, Dietary Compounds, Histamine, Nutrition, Vaccine

1. INTRODUCTION

COVID-19 (Coronavirus disease 2019) is a contagious disease spectrum caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection. SARS-CoV-2 is an infectious betacoronavirus first identified in humans in late 2019, in Wuhan, China. Despite efforts to prevent the spread of the virus, it was transmitted efficiently across the globe in record time, and Covid-

19 was declared a pandemic by the World Health Organization (WHO) in March 2020 (Malone et al., 2021; Ludwig & Zarbock, 2020). Since the beginning of the pandemic, measures have been taken to provide acquired immunity against the virus through vaccines. Large-scale phase III clinical trials of COVID-19 vaccines demonstrated their high effectiveness in preventing symptomatic COVID-19 infections. Evaluation of the safety, thermal stability, acceptable toxicity, duration of protective immunity, storage conditions, delivery system (oral, nasal, injection), dosing schedules and probable side effects of the COVID-19 vaccines was performed during the development of the vaccines (Farhud & Zokaei, 2021). Different types of vaccines, mainly attributing to messenger RNA (mRNA), DNA, inactivated, protein subunit, and vector vaccines, have been approved for human use. Although vector vaccines have been previously well-studied before the COVID-19 pandemic, their long-term effectiveness and methods to increase their production still remain debatable. The major hurdle for RNA vaccines is to enhance their stability throughout development, storage, and transportation. In the case of inactivated vaccines, the main issue is to boost their immunogenicity and efficacy (Kudlay & Svistunov, 2022). The efficacy of the vaccines approved for COVID-19 in reducing the severity of infection is quite significant. However, there have been reports of allergic reactions to COVID-19 vaccines that can potentially affect the quality of life (Nicaise-Roland et al., 2022). They mainly arise because of polyethylene glycol (PEG) and polysorbate excipients, which induce IgE-mediated reactions. Their clinical symptoms range from skin issues to life-threatening reactions, including anaphylaxis, notably in people having a history of allergies (Moghimi, 2021). The incidence of anaphylaxis following Pfizer BNT162b2 and Moderna mRNA-1273 vaccination was reported to be about 11.1 to 12.4 and 2.5 to 20.4 cases per million doses administered, respectively (Barbaud et al., 2022; Mahdiabadi & Rezaei, 2022). In addition, many of the adverse event symptoms associated with COVID-19 vaccines coincide with those of high histamine levels. Thus, innate immune responses and particularly high histamine levels are believed to be the cause behind most of the adverse events following COVID-19 vaccination (Ricke, 2022). A few examples of commonly reported adverse events after the first COVID-19 vaccine dose, according to a study, are flushing or erythema, dizziness or light-headedness, tingling, throat tightness, hives, and wheezing or shortness of breath. The allergic symptoms associated with the second dose of the vaccine are mild, self-limited, and/or resolved with antihistamines alone (Krantz, 2021). In order to address these adverse reactions, several studies have been reported with a better understanding of these events and their respective mechanisms. This review aims to describe these mechanisms as well as explore the intricacies of histamine intolerance, specifically in the post-COVID landscape, with emphasis on the risk factors that trigger this condition and examine the interlink between COVID-19 and histamine-related symptoms.

2. Histamine as a Central Mediator

Histamine is an endogenous biogenic monoamine synthesized from the amino acid L-histidine via a reaction catalyzed by the pyridoxal phosphate-dependent enzyme histidine decarboxylase (HDC) (Szukiewicz, 2024). It is a multifaceted proinflammatory and vasoactive mediator stored predominantly in the cytoplasmic granules of basophils and mast cells that is recognized for its role in managing different aspects of allergic reactions (Palestra et al., 2025). Histamine has a vital role to play in IgE-mediated anaphylaxis. Whenever the antigen-IgE complex binds to the high-affinity IgE receptor (FcεRI) on the surface of these cells, the stored histamine gets released immediately and reaches a reasonably high local concentration

(Moriguchi & Takai, 2020). Besides mast cells and basophils, histamine is also released when HDC is induced in non-mast cells at sites of tissue inflammation during the late and chronic phases of both allergic and non-allergic inflammation, thereby maintaining effective tissue histamine concentrations for extended periods and enabling the regulation of different functions through the production of cytokines, chemokines, and growth factors (Hirasawa, 2019). Histamine is known to increase the permeability of blood vessels, allowing white blood cells (WBCs) to enter tissues to promote inflammatory responses. (Huang et al., 2018). It exerts its pleiotropic effects on the skin and the respiratory, cardiovascular, digestive, immune and central nervous systems through its interaction with four known histamine receptor subtypes, namely, H1R, H2R, H3R and H4R (O'Mahony et al., 2011; Panula et al., 2015). These receptors are seven-transmembrane G protein-coupled receptors (GPCRs) differentially expressed on numerous immune cells, like mast cells, eosinophils, basophils, T and B cells, monocytes, dendritic cells, and macrophages. The pathobiology of allergic reactions can be influenced by the activation of histamine receptors on immune cells, which can modulate cytokine production and immunological responses (Palestra et al., 2025). Moreover, histamine amplifies allergic inflammation through H4 receptors and also promotes angiogenesis and fibrosis through H2 receptors (Hirasawa, 2019)-processes that may contribute to the spectrum of post-vaccination tissue-level reactions observed clinically.

With respect to vaccine-induced immunization, the commonly occurring reactions like fever, headache, exhaustion, muscle pain, and chills are mainly due to a rapid increase in the release of innate inflammatory cytokines (Weidensee & Sahu, 2025). Besides, it is to be noted that a proposed model of innate immune responses suggests that an acute surge in inflammatory molecules, including histamine, following vaccination may exceed the normal histamine tolerance threshold in susceptible individuals, leading to adverse effects. Symptoms resolve as histamine levels fall below the threshold. It is a hypothetical model that, if confirmed, would be able to predict that antihistamines, mast cell stabilizers, and diamine oxidase supplementation could reduce the incidence or severity of adverse effects across high-reactogenicity vaccines, including COVID-19 spike vaccines (Ricke, 2022).

3. Mechanisms of Vaccine-Induced Histamine Release

3.1. IgE-Mediated Type I Hypersensitivity Reactions

The classical allergic mechanism involves prior sensitization that results in the generation of antigen-specific IgE antibodies. When an allergen is first encountered, specific IgE is produced which binds to the type I high-affinity IgE receptors, FcεRI, on mast cells and basophils, thereby causing IgE-mediated anaphylaxis. If the cognate allergen or its closely related molecule is reencountered, mast cells and basophils get activated through IgE cross-binding on their surfaces, further promoting the release of inflammatory mediators like histamine, responsible for the symptoms of immediate hypersensitivity (Nicaise-Roland et al., 2022). Additionally, the main culprit in COVID-19 mRNA vaccines has been suggested to be excipients of vaccines including polyethylene glycol (PEG) that is generally found as a lipid conjugate in the nanoparticle coating. The specific IgE antibodies can recognize these excipients of the vaccines (PEG) and then bind to the FcεRI receptor on mast cells leading to their degranulation. These IgE antibodies are probably brought up by previous exposure to allergens in medicines, cosmetic products, aeroallergens or foods (Hung et al., 2022). Furthermore, the specific form of PEG is important. According to the study by Troelnikov et al, BNT162b2 vaccine and PEGylated liposomes, but not PEG alone in

its native state, could lead to substantial basophil activation (Troelnikov et al., 2021), highlighting that PEG-lipid conjugates are the true sensitizing antigens. However, anti-PEG IgE is not a predominant mechanism for anaphylaxis following mRNA COVID-19 vaccination (Zhou et al., 2023), pointing to the existence of other non-IgE pathways.

3.2. Complement Activation-Related Pseudoallergy (CARPA)

CARPA is a well-studied and recognized non-IgE mechanism triggered by nanoparticle surfaces activating the complement cascade. Anti-PEG IgM in the body binds to the liposome, forming a complex that activates complement through the classical complement pathway. The complement protein C5a is produced by a complement plasma protease activated by antibody complexes that has IgM. The most crucial mediators of complement activation are complement products including complement C3a, C4a and C5a, also known as anaphylatoxins. These anaphylatoxins stimulate mast cells, basophils and macrophages, thereby producing inflammatory mediators (Lee et al., 2023). It is to be noted that prior sensitization is not required for this process. A study reported the significant elevations in C5a, sC5b-9, and Bb but not C4d when Pfizer-BioNTech's Comirnaty and Moderna's Spikevax were incubated with 75% human serum. This suggests that C activation mainly occurs via the alternative pathway (Bakos et al., 2024). Moreover, this concept is also supported by research on animals- a small fraction of recipients of lipid nanoparticle-enclosed mRNA (LNP-mRNA) vaccines experience allergic reactions such as anaphylaxis following their initial or subsequent vaccinations. These reactions to I.V. administered liposomes are similar to CARPA (Dézsi et al., 2022).

3.3. MRGPRX2-Mediated Non-IgE Mast Cell Activation

Mas-related G-protein coupled receptor member X2 (MRGPRX2) is a class A GPCR expressed selectively on mast cells that can be activated by cationic compounds without being dependent on IgE. MRGPRX2 was discovered as the receptor that is responsible for non-IgE-mediated mast cell activation. MRGPRX2 is exclusively expressed on mast cells and shows varying affinity for numerous compounds like antimicrobial host defence peptides, neuropeptides, and even US FDA-approved drugs (Kumar et al., 2021). With respect to COVID-19 vaccines specifically, mast cell direct activation by positively charged substances such as iodinated contrast media, quinolones, or some neuromuscular blocking agents has been described through the MRGPRX2. It is also interesting to note that mRNA stabilization with PEG also gives a positive charge which may help enable this mechanism during COVID-19 vaccine reaction (Nicaise-Roland et al., 2022). However, direct evidence remains elusive. A study demonstrated that purified PEG and trometamol could not induce mast cell degranulation in an in *vitro* model for non-IgE-mediated hypersensitivity. Further research and studies utilizing complete vaccine formulations, lipid conjugates, and receptor gene variants are necessary to elucidate the mechanisms involved in vaccine hypersensitivity (Quan et al., 2022).

3.4. Cytokine-Driven Indirect Histamine Release

The immunogenic components of COVID-19 vaccines promote innate immunological activation that results in mast cell activation and histamine release. Adjuvants like LNPs that trigger inflammatory cytokines, including IL-1β and IL-6 are found in COVID-19 mRNA-LNP vaccines. Besides, these vaccines promote the synthesis of spike proteins which help in the release of inflammatory cytokines. Histamine released from mast cells during adverse allergic

events also plays a critical role in IL-6 secretion, which exacerbates inflammatory responses (Awaya et al., 2024). Clinical evidence of this feedback loop was documented in a severe case where mast cell activation symptoms started 24 hours after the mRNA-1273 booster vaccination with significant metabolic, lipidomic and cytokine derangements. Histamine concentrations peaked at life-threatening 18 ng/ml accompanied by high tryptase. Peak plasma IL-1Ra, IL-5, IL-6, IL-10, IL-11, CXCL10 and GM-CSF concentrations were elevated 54-, 4.9-, 85-, 54-, 6.1-, 19- and 6.4-fold respectively (Weiss-Tessbach et al., 2025). The bidirectional amplification loop between histamine and IL-1/IL-6 is well-characterized. Histamine enhances IL-1-induced IL-6 gene expression and protein synthesis via H2 receptors in peripheral monocytes (Conti et al., 2020).

3.5. Anti-PEG Antibody (IgG/IgM)-Mediated Complement Activation

Histamine release can also be triggered through complement activation driven by pre-existing or vaccine-induced anti-PEG antibodies of the IgG or IgM class, instead of IgE. This is different from the concept of Type I hypersensitivity. The CARPA phenomenon has been classified as a non-IgE-mediated pseudoallergy resulting as a consequence of the activation of the complement system. Evidence has emerged that suggests anti-PEG antibodies are present in people who most likely never took PEGylated drugs (Tenchov et al., 2023). The IgM subclass is very important since anti-PEG IgM is the primary cause of CARPA in liposomes. The production of anti-PEG IgM takes place through the proliferation and differentiation of certain B cells in the marginal zone of the spleen, and this process is independent of T cells (Lee et al., 2023). Additionally, IgG to different PEGs may play a role in rapid complement activation followed by degranulation of mast cells and basophils (Cabanillas et al., 2022). Notably, the study by Mouri et al. found that anti-PEG IgE-positive patients could tolerate a second dose of vaccine without any allergic reaction, further signifying that IgG/IgM-complement pathways and not IgE may dominate in various post-vaccine reactions (Mouri et al., 2022).

4. Clinical Manifestations of Histamine Release Following COVID-19 Vaccination

The clinical spectrum of histamine-mediated reactions following COVID-19 vaccination ranges from mild cutaneous symptoms to severe systemic anaphylaxis. Vaccine-associated allergic responses may have an impact on any part of the body, including the skin, respiratory, cardiovascular and gastrointestinal systems. Flush, pruritus, urticaria, angioedema, facial edema, tachycardia, dizziness, sneezing, itchy nose, wheezing, chest tightness, laryngeal edema, nausea, vomiting, abdominal pain, and diarrhea are a few mild-to-moderate allergic reactions that are generally local and non-anaphylactic (Kim et al., 2021). Towards the end of the clinical spectrum, anaphylaxis manifests as dermatological (urticaria, flushing, angioedema), respiratory (stridor, cough, wheeze, shortness of breath) and gastrointestinal (nausea, emesis, abdominal pain, diarrhea) symptoms due to the effects of histamine and other mediators on the target organs. Asphyxiation from upper airway angioedema, acute bronchospasm or hypotension are some of the causes that may lead to anaphylactic deaths (Kelso, 2021). The timing of onset is variable and mechanistically informative. According to a study, it was found that the onset time of urticaria and/or angioedema varied post-mRNA COVID-19 vaccination (less than 4 hours; 25% ≤1 hour). The onset of urticaria and/or angioedema was also delayed (more than 24 hours) and occurred between 4 and 24 hours after immunization (Anvari et al., 2023). Complement-driven histamine release is specifically linked to urticaria formation since C5a generation promotes mast cell degranulation and histamine release, thereby leading to vasodilation,

extravasation, wheals, as well as angioedema (Kocatürk et al., 2023). Notably, delayed urticarial reactions, although distressing, typically have a more benign course. In individuals living with pre-existing mast cell abnormalities, the response can be significantly intensified. Following mRNA-1273 booster immunization, a study revealed that the peak plasma IL-6 concentrations increased 85-fold, whereas histamine concentrations peaked at a potentially fatal 18 ng/ml along with high tryptase (Weiss-Tessbach et al., 2025). From a pathophysiological perspective, certain mediators, including histamine, proteases and leukotrienes, prostaglandins may cause an increase in mucus production, bronchial smooth muscle contraction, vasodilation, and also vascular permeability (Sobczak & Pawliczak, 2022).

5. Conventional Management of COVID-19 Vaccine-Induced Histamine-Mediated Reactions

The approach to managing vaccine-induced histamine-mediated allergic reactions is determined by the seriousness of the adverse events that might occur following vaccination. In case of acute anaphylaxis, epinephrine must be administered immediately as the primary treatment without any delay. Antihistamines and corticosteroids have a limited role to play in the management of anaphylaxis and must not be considered as the initial treatment choice; however, oral antihistamines are suitable for mild to moderate skin allergies such as urticaria (Khalid & Frischmeyer-Guerrerio, 2023). For high-risk patients such as those with mast cell disorders, a structured premedication regimen involving H1 and H2 antihistamines administered 1 hour prior and also montelukast, given 24 and 1 hour before vaccination, must be implemented while being under the observation of an allergist for 30 minutes (Rama et al., 2022). Routine premedication is not advocated for the general population because there is no evidence supporting either the benefit or the requirement for premedication or graded dosing (Greenhawt et al., 2023). In case of patients who require re-vaccination following a previous adverse reaction, pretreatment with omalizumab has shown good potential. In a study, two subjects pretreated with a single dose of 300 mg of omalizumab before the second vaccination did not experience either angioedema or urticaria as immediate responses (Guzmán-Pérez et al., 2021). Reassuringly, among 159 subjects who reported immediate allergic reactions, including 19 experiencing anaphylaxis after their first dose of vaccination, only 20% exhibited moderate allergic symptoms following their second dose, with no subject experiencing anaphylaxis (Khalid & Frischmeyer-Guerrerio, 2023).

6. Side Effects of Pharmacological Agents Used in the Management of COVID-19 Vaccine-Induced Allergic Reactions

Potential allergic reactions to COVID-19 vaccines range from mild contact dermatitis or urticaria/hives all the way up to life-threatening anaphylaxis. Pharmacological treatment options for COVID-19 vaccine-related allergic reactions include medications with known potential side effects. Epinephrine is usually administered as early as possible in the treatment of anaphylaxis. But, there is some reluctance to use epinephrine due to its association with cardiovascular adverse events (Kamath et al., 2025). Its stimulation of all α and β adrenergic receptors causes short-term increases in systolic blood pressure, hyperglycemia, and other features of metabolic syndrome (Ziegler et al., 2012). Besides, H1 and H2 antihistamines are both commonly used in clinical settings. However, there have been some reports regarding differences in effectiveness as well as adverse reactions, some of which are rare and potentially serious. Research has shown that gene polymorphisms account for differences in the efficacy of antihistamines. These include polymorphisms of those genes responsible for encoding metabolic enzymes, drug transporters, and drug

targets. Additionally, genes that play a role in the development and progression of the disease itself may affect individual responses to antihistamine treatment (Li et al., 2022). The first-generation H1 antagonists are lipophilic drugs that can cross the blood-brain barrier easily. They activate both central and peripheral H1 receptors, producing effects on the central nervous system (CNS). These CNS effects include sedation, psychomotor impairment, and anticholinergic side effects. Second-generation H1 antihistamines are more selective for peripheral receptors and exhibit minimal central penetration, making them safer with reduced sedative potential (Farzam et al., 2023). Corticosteroids are anti-inflammatory and immunosuppressive drugs that have been used since the 1950s to treat asthma, allergy, rheumatoid arthritis and dermatological diseases (Ciriaco et al., 2013). However, as many as 20% of patients taking high doses of corticosteroids develop depression, mania or psychosis that necessitates pharmacotherapy, while 75% complain of psychiatric symptoms that resolve when drug treatment is stopped (Ciriaco et al., 2013). A systematic review and meta-analysis determined moderate certainty evidence that a short-course (≤14 days) of systemic corticosteroids use in a paediatric population had an increased risk of small absolute harms for nonserious hyperglycemia and sleep issues. Corticosteroids use also led to increased risk of gastrointestinal bleeding with low certainty evidence (Lima et al., 2025).

7. Role of Dietary Bioactive Compounds in Managing Allergic Reactions to COVID-19 Vaccines

Dietary bioactive compounds such as omega-3 fatty acids, vitamin D, curcumin, ginger, quercetin, and epigallocatechin gallate (EGCG) have been shown to modulate Th2 responses, stabilize mast cells, and attenuate IgE/cytokine-driven inflammation. These compounds hold preclinical and early clinical promise for allergy prevention, though more rigorous, standardized clinical trials are necessary (Zafrilla et al., 2025). COVID-19 vaccine-induced allergic reactions, however, result from IgE- and non-IgE-mediated mast-cell activation secondary to vaccine excipients such as PEG and polysorbate 80. Managing these reactions is currently confined to clinical interventions like epinephrine, antihistamines, or corticosteroids (Turner et al., 2021; Unsal et al., 2021). Although quercetin and EGCG are known mast-cell stabilizers, their direct relevance to vaccine reactions has not been clinically established, leaving them as subjects of theoretical interest only. Both quercetin and EGCG have been proven to be protective against allergy at the cellular level- quercetin blocks calcium influx and FcεRI-associated signaling in IgE-activated mast cells (Mlcek et al., 2016; Zhao et al., 2024). EGCG, on the other hand, inhibits mast cell degranulation and calcium influx via a related, yet distinct pathway (Kim et al., 2020). Allergy and vaccine hypersensitivity may look alike on the surface. Both of these mechanisms end in a flushed, itching, histamine-driven storm, but, they often begin at completely different pathways, and bridging that gap will require more focused clinical trial research.

8. CONCLUSION

Vaccines against COVID-19 can cause histamine-mediated hypersensitivity reactions through various mechanisms, including IgE-mediated allergy to PEG-lipid conjugates, CARPA, MRGPRX2 activation, and cytokine-induced mast cell activation. These reactions can range from mild skin allergies such as hives to life-threatening anaphylaxis. Treatment options include antihistamines and corticosteroids. However, these medications are associated with side effects. For this reason, functional nutrition could be considered as an adjunct approach to mitigate risk. Nutrients such as quercetin, curcumin, vitamin C, vitamin D, zinc, magnesium, and omega-3 fatty acids may help suppress allergic reactions post vaccination. Administration of these

nutrients under the guidance of a healthcare professional could potentially decrease the risk of allergic reaction in predisposed individuals. This approach is not meant to replace life-saving emergency medical care in the event of anaphylaxis. Understanding each individual's risk of reaction before vaccination is critical. Existing research investigating underlying mechanisms of these vaccine reactions should be continued. Assessing micronutrient deficiencies and mast cell activation could be used in conjunction with existing prevention strategies to improve functional nutrition before vaccination in high-risk individuals. Due to overlapping mechanisms between COVID-19 vaccines and future vaccines created with LNPs, these strategies will likely be useful for preventing reactions to future vaccines too.

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