Understanding Allergies from Molecular Mechanisms to Personalized Treatment Strategies

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Abstract

Millions of people globally suffer from allergy symptoms yearly, with minor symptoms like sneezing to more severe symptoms like anaphylaxis. Allergy reactions are defined as the immune system's adverse reaction to harmless substances. This report discusses the mechanism of allergic reactions, the prevalence of different allergies, and the risk factors associated with allergy development. This review will also include the current solutions to allergies, including pharmaceutical treatments, therapeutics, and preventative treatments. With this overview, we aim to provide practical guidance to patients and caregivers in managing allergies with the ultimate goal of improving public health outcomes.

Introduction

Despite our society becoming increasingly hygienic as technology advances, in recent years the number of allergy patients has been on the rise. According to the Center for Disease Control (CDC), a third of U.S. adults and a quarter of U.S. children were diagnosed with seasonal allergy, eczema, or food allergy in 2021 (*More Than a Quarter of U.S. Adults and Children Have at Least One Allergy*). An allergic reaction is the result of our immune system producing an inappropriate immune response to harmless substances called allergens. Allergens include respiratory particles like dust mites, animals, pollen, and mold; consumed allergens like peanuts, tree nuts, and soy; insect stings are also a common type of allergen that does not fall under the two categories above (“Types of Allergens”). Unlike others, some individuals' immune systems mistakenly perceive allergens as harmful, leading to a range of allergic symptoms. Mild symptoms include sneezing, coughing, itching, and swelling, while severe reactions such as anaphylaxis–difficulty breathing due to airway constriction–can be life-threatening (“Anaphylaxis”; “Overview: Allergies”).

Allergies can develop due to a variety of factors. Some people might have a higher risk of developing allergies due to hereditary aspects, meaning they have a family history of allergies (Aldakheel). Others may have been born or have inherited specific genes like MALT1 in their DNA that cause them to be more inclined to have an allergy than others. But even if we disregard these genetic and hereditary aspects of allergies, allergies can also develop due to other external factors: drastic changes in allergen exposure, the route of exposure, and environmental factors like pollution (Aldakheel).

As of now, allergy treatments include medications like antihistamines and steroids, which help treat symptoms immediately (Aldakheel). In addition, monoclonal antibody injections called Xolair, immunotherapy, and even parasitic worm infections are options that help suppress allergic reactions or even get rid of them in the long term (“FDA Approves First Medication to Help Reduce Allergic Reactions to Multiple Foods After Accidental Exposure”; “Why Catching a Parasite Might Be the Best Thing for Your Allergies”; Frew). Preventative treatments are also available; such as early exposure to allergens and avoiding allergens (“Overview: Allergies”; Trogen et al.).

This report will review the biological underpinnings of allergies, the prevalence of different allergies, and the risk factors that cause allergy development. It will also cover currently available solutions to allergies and emerging preventative treatments. Understanding the

complexities of allergies, their prevalence, and the factors influencing their development is crucial for improving outcomes and quality of life for allergy sufferers worldwide.

Mechanism Behind Allergies

Allergies are triggered by errors in the immune system, which is the key defense system in our body that fights off diseases to prevent people from falling ill. One of the most important actions in this defense system is recognizing whether a substance is potentially harmful. If the substance is harmful, the system will prepare an attack to fight off the substance, releasing an immune response tailored to it. In the case of an allergic reaction, that substance is called an allergen.

Once the immune system misidentifies the allergen, an immune response is released to attack it and prime the sensitization process. By the end of the response, the immune system produces specific antibodies–often IgE for allergens–targeted to the allergen; these antibodies are the immune system's main tools of defense when they attack specific antigens (Aziz et al.). These antibodies then bind to immune cells responsible for releasing inflammatory chemicals. At this point, we say that the body is sensitized to the allergens. In other words, the IgE antibodies that target the allergen are present and ready to launch a full-on allergic reaction whenever the allergen is encountered again. During the subsequent exposure to the allergen, we experience typical allergy symptoms like swelling in the skin, runny noses, and watery eyes due to the release of inflammatory chemicals.

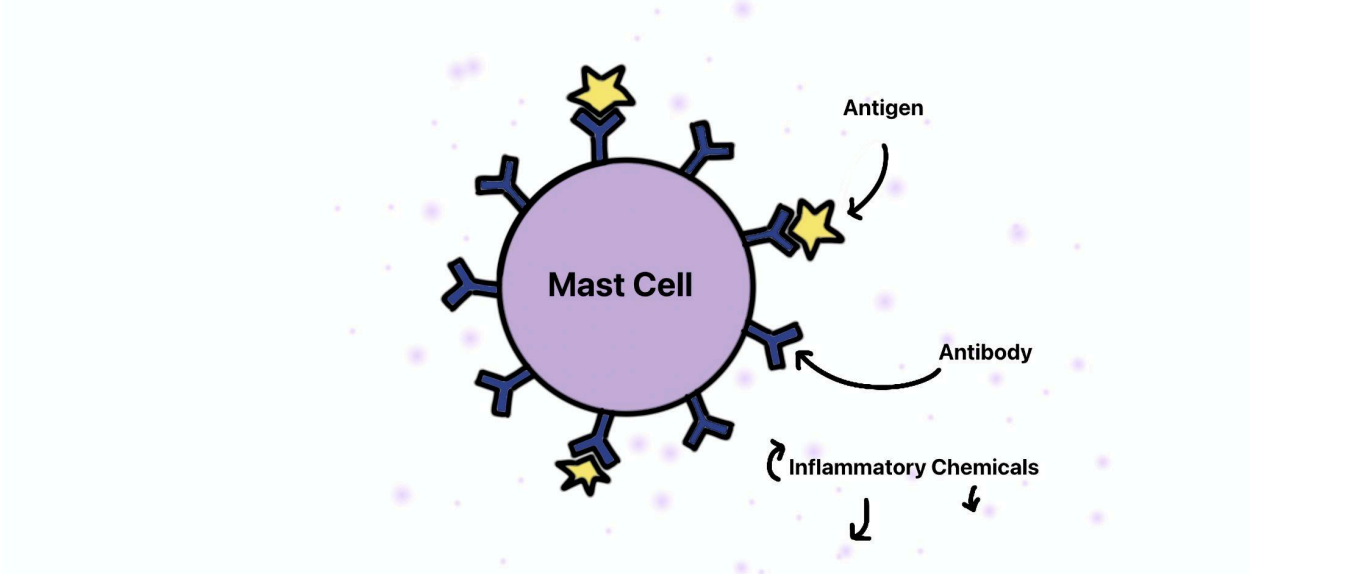

Fig 1. Antigen encounter after sensitization
When the body encounters the allergen after sensitization, an inflammatory response is released as the allergens trigger the release of inflammatory chemicals by binding onto the antigen on the mast cell's surface.

Allergens that cause these reactions can be anything (Aldakheel). Some can be from foods, animals, plants, insects, or even from the air, like pollen ("Types of Allergens"). When these allergens are inhaled, consumed, or absorbed into our skin, there is always a chance that the immune system might become sensitized to them. Some allergies are more common than others because we have more exposure to them (Galli et al.). For example, pollen allergies like

tree, grass, and weed allergies are common because every year, we are exposed to pollen produced by these flourishing plants all around us (James). During this season, the immune system has a greater chance of being sensitized to the pollen by frequent exposure ("Overview: Allergies"). Now that we understand the basics of how allergies develop, we can then dive into risk factors and treatments of allergies with greater clarity.

Risk Factors for Allergy Development

There are multiple risk factors associated with allergy development. They can be developed due to eczema, a skin condition that increases its vulnerability to skin infections, changes in exposure to the allergens, or from air particles in the environment we live in (Aldakheel; "Why Do I Have Allergies after Moving to a New Place?"; "Risk Factors for Food Allergy"; *Eczema (Atopic Dermatitis)*). Principally, all allergies are developed when our immune system becomes sensitized to an allergen; and for sensitization to occur, we must be exposed to an allergen in some way. During these exposures, a misinterpretation of the allergen by the immune system can lead to its development. The primary risk factors include: 1) changes in exposure to allergens, 2) route of exposure, 3) environmental factors, 4) inheritance, and genetics.

1) Changes in exposure to allergens: There is a greater chance of allergen sensitization when the body is deprived of an allergen and exposed to it after several years ("Why Do I Have Allergies after Moving to a New Place?"). Due to the drastic change, the immune system's sensitivity rises and causes greater difficulty in determining whether the allergen is harmful or not during the sudden exposure. This can be observed when we compare allergy prevalence to those in urban areas and rural areas (Tizek et al.). People who live in rural areas are consistently exposed to many bacterial and viral substances from their outdoor environment. The constant exposure to these substances causes people to become desensitized to them, lowering the likelihood of the immune system to stimulate an immune response against them (Tizek et al.). In contrast, those living in urban areas are often protected from these foreign substances in nature. Consequently, their immune systems are much more vulnerable to release a response to a sudden exposure to a foreign substance (Tizek et al.). In a way, one can say that a person born in a rural area has an immune system that is better trained compared to those in urban areas (Tizek et al.). The same can also happen when people migrate from one area to another (Amoah et al.). For example, when a person raised in a cold region with a lower pollen count for several years moves to a much warmer region, his or her immune response might be triggered to stimulate an immune response towards pollen because it has never been precedent to it.

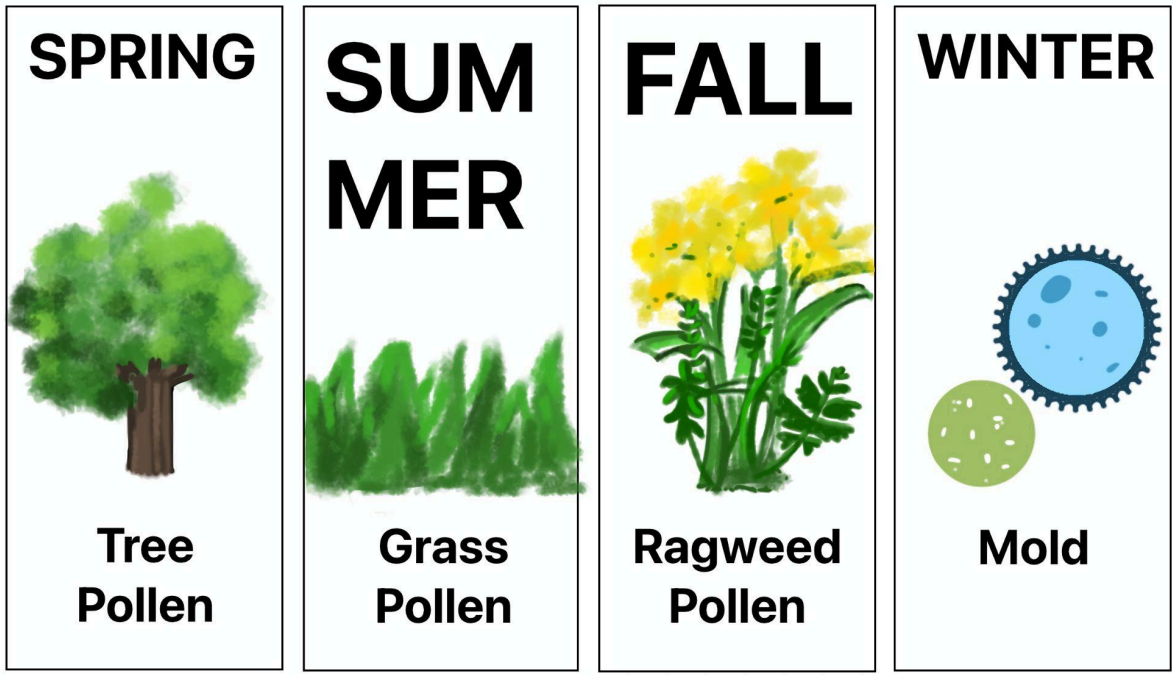

Fig 2. Common Types of Seasonal Pollen: Not all pollen allergies are caused by the same type. In different seasons, there are seasonal allergens more common than others. For this reason, when a person migrates from a place that is cold to a place with four distinct seasons, they may encounter new types of pollen that his or her body is not used to.

2) Route of exposure: Along with the changes in exposure, the routes by which the allergens enter a body also play a key role in allergy development ("Risk Factors for Food Allergy"). Usually, allergens enter our body through inhalation or consumption. However, eczema patients can also be exposed to allergens through their skin ("Risk Factors for Food Allergy"). Due to their dry skin, eczema patients have weaker skin barriers. Since the skin acts as the first line of defense against foreign substances, eczema patients' skin is more prone to allergen invasion than others.

Some even connect this new exposure route to a risk for food allergy development (Papapostolou et al.). For example, food allergens are usually consumed orally. This is considered the usual route to both us and to our immune system. But when these food allergens are introduced through an eczema patient's skin, the abnormality of this route raises a higher risk of sensitization ("Risk Factors for Food Allergy"). The prevalence of food allergies is 33% to 39% in severe eczema patients while it covers 0.1% to 0.6% of the general public (Papapostolou et al.). For this reason, eczema can be seen as a risk factor of food allergy development.

3) Environmental factors: Another risk factor promoting allergy development is pollution. In addition to exposure patterns to airborne allergens, gaseous pollutants like nitrogen oxide, produced by factories and cars, also increase the likelihood of developing sensitization to airborne allergens (Aldakheel).

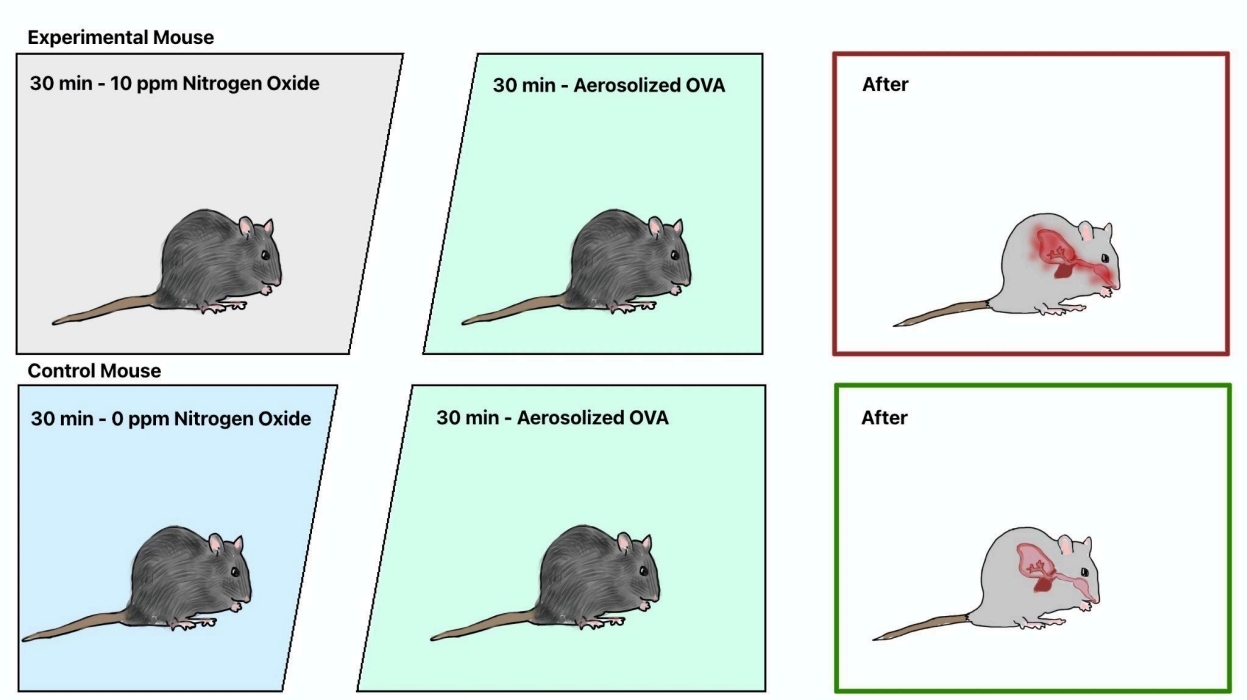

Fig 3. Mice Experiment on Nitrogen Oxide's Effect on Sensitization
In the experiment, the experimental group of mice that were exposed to nitrogen oxide ended up with inflammation in their airways. In contrast, the control group of mice did not show any signs of adverse reactions (Bevelander et al.).

To study the correlation between allergy development and nitrogen oxide exposure (Bevelander et al.). Researchers tested with two groups of mice, the experimental group was exposed to aerosolized ovalbumin (OVA)–a common protein used in research–and nitrogen oxide and the control group was only exposed to aerosolized OVA. Since purified OVA–a harmless protein found in egg whites used to study immune responses–does not generally provoke an immune response, researchers studied whether nitrogen oxide affected allergy development to OVA. The experimental group of mice was administered an hour of nitrogen oxide before being exposed to aerosolized OVA for thirty minutes. The control group was placed in room air free of nitrogen oxide before the thirty-minute exposure to aerosolized OVA. By the end of the experiment, researchers observed that the mice that had undergone nitrogen oxide exposure had evident airway inflammation present. On the contrary, the control group of mice did not exhibit any signs of airway inflammation during observations. Through the inflammation observed in the experimental mice, the study concluded that nitrogen oxide promoted allergic sensitization to airborne allergens (Bevelander et al.). Connecting this study to humans, in Mexico City, many children with asthma–a lung disorder that causes difficulty breathing due to airway inflammation–demonstrated a high correlation between respiratory symptoms and pollution caused by traffic (Aldakheel). Since asthma can also be triggered by airborne allergens, we can hypothesize that airborne allergies would also be greatly affected by pollution. For this reason, people, especially those at a higher risk, are advised to avoid living in areas with poor air quality to prevent airborne allergy development.

4) Inheritance and Genetics: Though there are many external factors that may trigger the development of an allergy, allergies can also be triggered by genetics. In the immune system,

MALT1 is identified as a key regulatory protein in the immune response. A person with a defective MALT1 gene is often considered immunodeficient meaning they have defected immune responses (Jaworski and Thome). In a study, National Institute of Allergy and Infectious Diseases (NIAID)-funded researchers concluded that among the subjects who had not consumed peanuts before the age of five, those who had a gene called MALT1 tended to have a higher risk of developing peanut allergies in comparison to those that did not have the gene ("Risk Factors for Food Allergy"). Initially, the study Learning Early About Peanut (LEAP) focused on peanut allergy prevalence by experimenting with allergen exposure timing (Trogen et al.). Among a group of high-risk infants, one group had peanuts before the age of five while the other group avoided them. Although the early exposure proved effective by ending up with fewer children with peanut allergies, researchers realized that even within this group, MALT1 was associated with provoking an antibody, IgE, response to certain proteins in peanuts (Winters et al.). In addition to the consumption group, MALT1 carriers within the avoidance groups showed higher levels of IgE compared to non-carriers. Through these observations, we can see how MALT1 ties to peanut allergy development (Winters et al.). Through the interplay between genes and peanut allergy development, we can see how nobody is born with allergies, but some others are born with a greater risk of developing allergies compared to others.

With genetics being a risk factor, allergies can be inherited. Children born under allergic parents have higher immune system sensitivity compared to those born from non-allergic parents. Even if only one person is allergic, the chances that their children would develop an allergy is around 30-50% (Aldakheel). While children with both non-allergic parents have only a 12% chance of developing an allergy (Aldakheel). Many risk factors contribute to allergy development. They can be inherited, exhorted by certain genes, triggered by conditions like eczema, or provoked by environmental factors. With many risk factors causing allergies, allergy patients can be seen all around us.

Pharmaceutical Treatments

Pharmaceutical treatments are one of the most accessible forms of solutions to immediately alleviate allergic symptoms like inflammation, hives, swelling, rash, congestion, watery eyes, and breathing problems ("Overview: Allergies"). Treatments can be in the form of pills, liquids, nasal sprays, inhalers, eye drops, skin creams, and shots ("Allergy Medications: Know Your Options"). Depending on the medication, some may need a prescription from the doctor, while others can be bought in drugstores. In this section, we will go over 1) antihistamines, 2) corticosteroids, and 3) Xolair injections (Aldakheel; "FDA Approves First Medication to Help Reduce Allergic Reactions to Multiple Foods After Accidental Exposure").

1) Antihistamine: Antihistamines are drugs that are used to treat symptoms caused by histamine (Farzam et al.). Some common antihistamines in the drugstore include Allegra, Claritin, and Zyrtec ("Antihistamines"). Though antihistamines can be used to treat many different types of allergy, they are generally used to treat allergic rhinitis: an atopic disease that often proposes nasal irritation to inhaled allergens (Akhouri and House). To understand how antihistamines work, first, one must know about histamines and how they work. Histamines are chemicals released during an allergic reaction that promote inflammation and blood vessel dilation. As chemical messengers, histamine binds to receptors to initiate the swelling from the allergic reaction. To counteract this effect, antihistamines bind to these same receptors, preventing histamines from attaching and initiating an allergic response (Farzam et al.). With the

lack of receptors available for histamines, allergic symptoms induced by histamines are reduced.

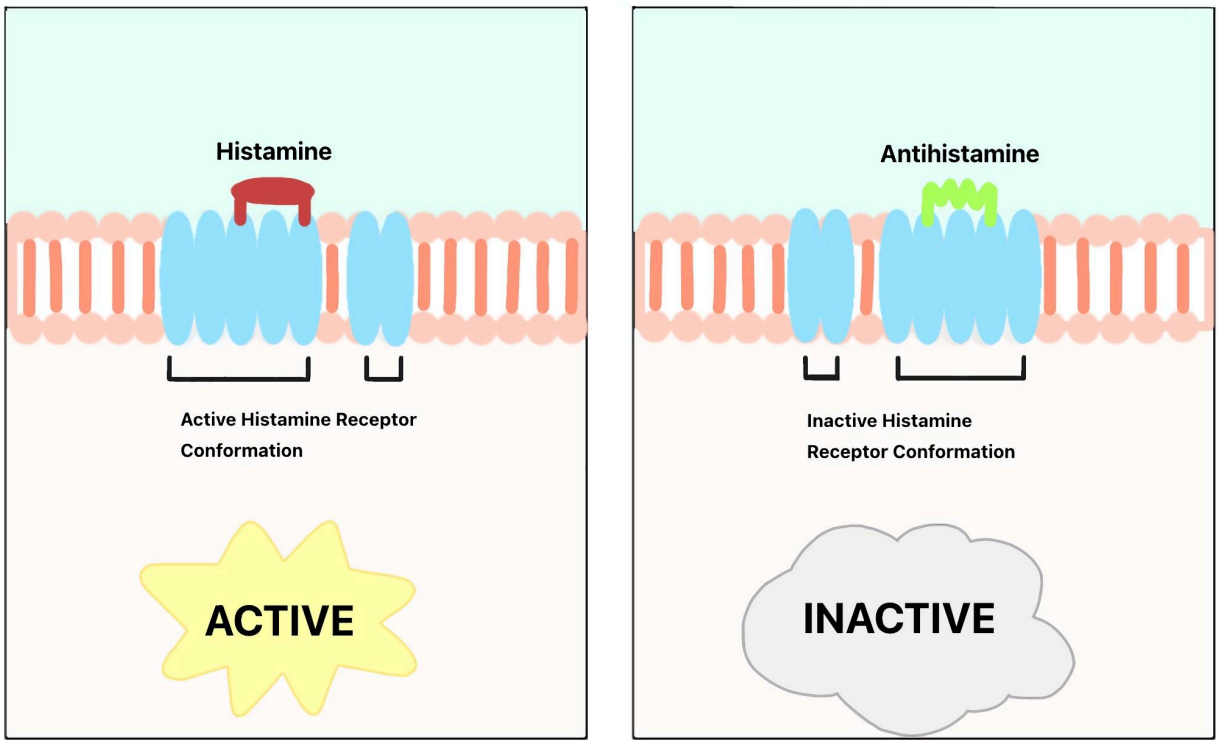

Fig 4. Cellular Histamine and Antihistamine Mechanisms
While histamine activates the receptor to create inflammation in the body, antihistamines give the opposite effect. Though they both bind to the same receptor, antihistamines deactivate it to prevent the body from producing an inflammatory reaction.

But along with the ease that antihistamines provide, there are also some side effects to it. For instance, users sometimes experience a dry mouth, dizziness, insomnia, and drowsiness. When the dose increases, delirium and decreased coordination are also experienced (Farzam et al.).

2) Corticosteroids: Corticosteroids are man-made steroid hormones that mimic the properties of glucocorticoids and mineralocorticoids produced in the adrenal cortex (Hodgens and Sharman). In our lives, they are commonly found in drugs like Nasonex, Prelone, and Medrol (“Allergy Medications: Know Your Options”). Corticosteroids are a type of medication often used to treat allergic rhinitis and anaphylaxis. When corticosteroids are administered to the body, they bind onto the glucocorticoid receptor and take effect at the nucleus, inhibiting the production of inflammatory cells and immune cells responsible for producing an inflammatory response. Through this process, allergic symptoms due to inflammation and the overall immune system become suppressed (Hodgens and Sharman).

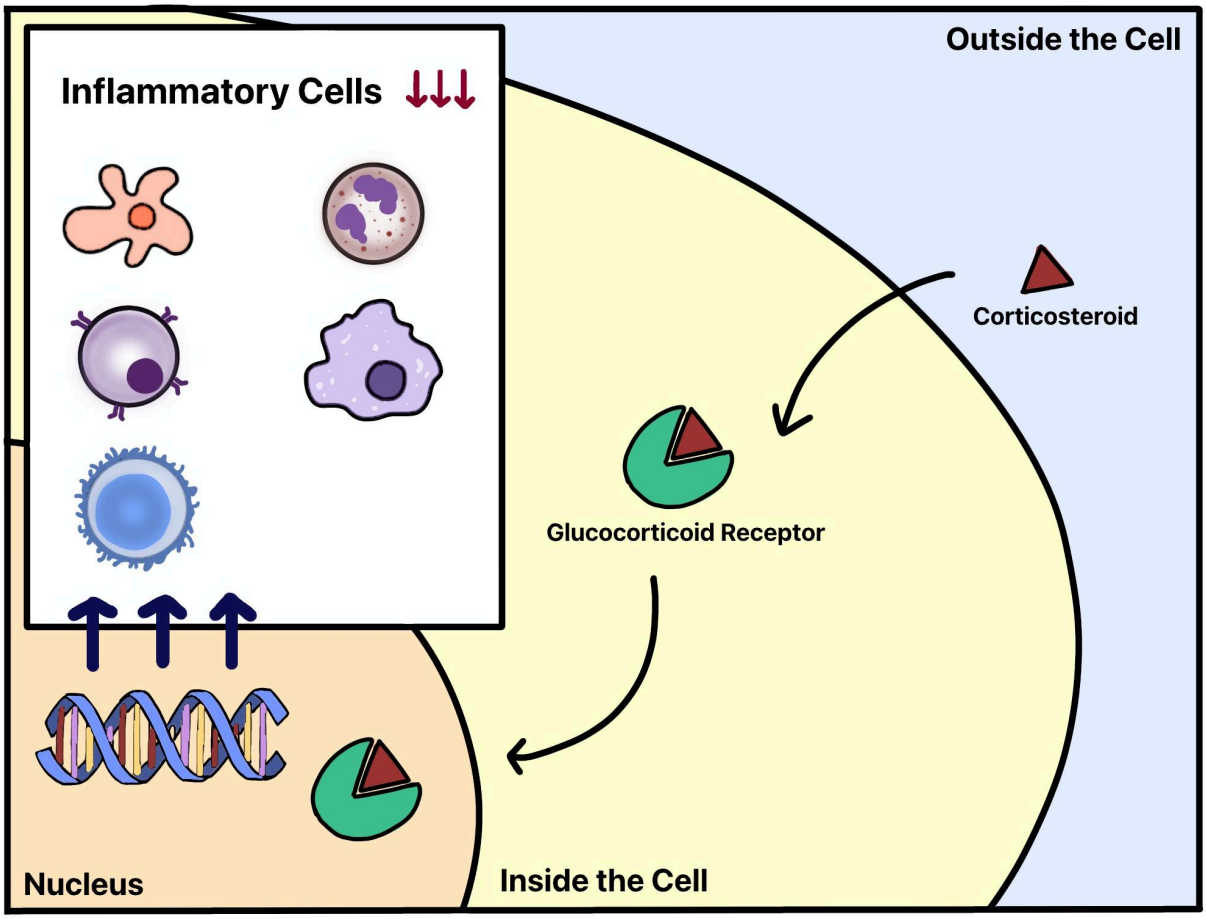

Fig 5. Corticosteroid Function
Up above is a brief process of how corticosteroids alleviate allergic reactions caused by inflammation. Corticosteroids enter the body and bind to the glucocorticoid receptors inside the cell. This then takes effect into the nucleus, where the production of inflammatory cells is inhibited, leading to a dampened allergy response.

In general, corticosteroids taken at a normal dose and duration do not carry many side effects. However, when they are given at higher doses with greater frequency, corticosteroids can cause many adverse effects in the body. Some of the common side effects include weaker bones and muscles, diabetes development, and impaired immune function (Hodgens and Sharman). Among these, impaired immune function is especially unavoidable since corticosteroids reduce inflammatory responses by suppressing the entire immune system. This causes the body to be susceptible to infections due to the body's weakened defense system against viruses and bacteria (Hodgens and Sharman).

3) Xolair Injections: Xolair monoclonal antibody injection binds onto IgE–an antibody that triggers an allergic reaction–and prevents it from binding into its receptors ("FDA Approves First Medication to Help Reduce Allergic Reactions to Multiple Foods After Accidental Exposure"). Unlike the previous options, Xolair injections are not used to provide immediate relief to allergic reactions. Instead, they are intended to reduce the severity of allergic reactions in the case of accidental exposure to food allergies. This makes them particularly useful for allergy patients who come across life-threatening situations during allergic reactions. Common side effects of

Xolair injections are reactions at the injection site and fever. Besides the side effects, there were also cases of anaphylaxis upon administration of Xolair injections. Subsequently, although self-injections are approved (Murphy et al.), it is recommended that Xolair injections are given in a healthcare setting well equipped to prepare for anaphylaxis ("FDA Approves First Medication to Help Reduce Allergic Reactions to Multiple Foods After Accidental Exposure").

Therapeutics

For several years, we have thought that allergies had no cure. For this reason, most people focus on treating their symptoms with the pharmaceutical treatments mentioned above. But through further research, we developed more options that help reduce or even get rid of allergy symptoms in the long run. One of them is immunotherapy (Aldakheel), which can be divided into two types: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) (Incorvaia et al.). The other is administration of parasitic worms. In this section, we will go over these three therapeutic methods to improve allergic symptoms in the long run.

1) Immunotherapy: During allergy immunotherapy, patients are given increasing doses of allergens to improve their immune system's tolerance towards them. As the immune system is consistently and frequently exposed to the allergen, it slowly becomes desensitized to the allergen and suppresses IgE antibodies involved in allergic reactions (Aldakheel). Immunotherapy can be administered subcutaneously or sublingually. Although both of them follow the same concept, subcutaneous immunotherapy is injected under the skin while sublingual immunotherapy is administered orally under the tongue (Boltansky).
    a) Subcutaneous Immunotherapy: Subcutaneous immunotherapy is more commonly known as allergy shots ("Allergy Shots - What You Need to Know"). Allergy shots are commonly used to treat allergic rhinitis and insect venom allergies. At the injection site of the allergy shot, local reactions like redness and swelling can be commonly found among patients. More severe reactions are systemic reactions like wheezing, coughing, flushing, or tightness of the throat can also occur. Due to this, patients who receive an allergy shot are required to stay in the office for thirty minutes to watch out for these symptoms ("Allergy Shots - What You Need to Know").
    b) Sublingual Immunotherapy: Sublingual immunotherapy can be in the form of a tablet or an allergy drop (Boltansky). While the tablets work better for airborne allergens like ragweed pollen, grass, and house dust mites. Allergy drops are also effective with trees, cats, and dogs, and feathers as well. Both options can be administered at home. For this reason, sublingual immunotherapy gets rid of the hassle of reaching out to the clinic for every drop or tablet. But even if they can be taken at home, sublingual immunotherapy may also have some moderate symptoms in the first few weeks like skin reactions, oral irritation, nausea, or itching eyes. However, the chances of having a severe allergic reaction like anaphylaxis are extremely rare (Boltansky). An advantage of sublingual immunotherapy is that it can also be used against food allergies. In 2003, a kiwi-allergic patient was successively desensitized after taking increasing amounts of kiwi extract (Schworer and Kim). As the immunotherapy continued, the number of specific IgE antibodies decreased in the patient's system. Moreover, when the patient resumed immunotherapy after four weeks of rest, the patient did not have

any side effects (Schworer and Kim). Through this case, sublingual immunotherapy might be a rising option for treating food allergies in the future. For the best effects, both sublingual and subcutaneous immunotherapy should be done for at least three to five years (Boltansky; “Allergy Shots - What You Need to Know”).

2) Parasitic Worms: Yes, parasitic worms are a type of parasite that can cause the same harm as a virus or bacteria. However, in the context of an allergic person, parasitic worms present surprising benefits for allergy symptoms (“Why Catching a Parasite Might Be the Best Thing for Your Allergies”). When a parasitic worm enters the body, the immune system identifies them as a foreign invaders and attempts to release an immune response. In response to the immune system, parasitic worms release messengers intended to shut down the immune cells in action. Subsequently, the immune system weakens, allowing the worms to survive inside the body. Though this may alert many people, the weakened immune system also makes them less sensitive to allergens. Coming back to allergies, the immune system’s hypersensitivity is the cause of an allergic reaction. Therefore, when the immune system is down, they would not be as reactive to an allergen. But despite this notion of parasitic worms helping allergy symptoms, there are many risks and downsides. One of them is malnutrition. Without the immune system attacking them, parasitic worms settle in the intestines to absorb the nutrients in our body to survive (“Why Catching a Parasite Might Be the Best Thing for Your Allergies”). Further research and experimentation are needed to fully understand the impact of parasitic worms on overall health, particularly in the context of allergy treatment.

Preventative Treatments

Although treating existing allergies is also important, learning how to prevent them from developing is also crucial. Especially with the number of allergy patients increasing globally each year, there must also be future parents who want to prevent their children from developing an allergy as well. One thing we need to understand here is that people are not born with allergies. Even though there may be some individuals more susceptible to allergies due to hereditary factors, there are ways to lower the likelihood of developing them. For instance, food allergies can be prevented by early allergen exposures, while allergen avoidance prevents allergies to animals (Trogen et al.).

1) Early Exposure: Previously, we have touched on the LEAP study (Trogen et al.). LEAP is the first study that suggested early introduction to allergens to prevent allergy development. In this study, one group of high-risk infants was given increasing amounts of peanuts in their diet during four to six months of age. To compare the outcomes, the other group of infants avoided peanuts during the same period. When the participants were tested for peanut allergies back at the age of five, the prevalence of peanut allergies decreased by approximately 80% compared to those who avoided peanuts. Though this part of the study was enough to convince people about the power of early exposure, a new study, Persistence of Oral Tolerance to Peanut (LEAP-On) proved that the peanut tolerance built from the early exposure persisted even when the peanut consumption paused for a year (Trogen et al.). With LEAP and LEAP-On highlighting the idea of early exposure, it is now advised that other allergens like eggs, milk, and fish (Chin et al.).
2) Allergen Avoidance: Though there are some allergens that are better off in early exposures, there are some others where simply avoidance is the answer. This option

may help prevent allergies caused by cats and dogs (“Overview: Allergies”). While it is practically impossible for airborne allergens like pollen. After all, avoiding allergens does not give the immune system a chance to become sensitized in the first place. Even if avoidance may not be best in prevention, in the case of people who are already allergic, avoidance also prevents allergic symptoms from occurring.

Conclusion

Many people around us suffer from allergies every day. Due to the watery eyes, coughs, nasal irritation, and even anaphylaxis, the quality of their lives is constantly nagged by rising pollen levels, foods to look out for, or animals and insects that cause a fuss to their immune system (“Types of Allergens”; “Overview: Allergies”). Although our immune system was simply trying its best to protect us from potential danger, it ended up mistakenly attacking allergens that are technically harmless in reality. In addition, risk factors like inheritance, genetics, air pollutants, changes in allergen exposures, and eczema promote our chances of developing allergies (Aldakheel; “Why Do I Have Allergies after Moving to a New Place?”; “Risk Factors for Food Allergy”).

To treat patients with allergies, healthcare providers offer pharmaceutical solutions such as antihistamines, corticosteroids, and Xolair injections to relieve allergic symptoms (Hodgens and Sharman). A therapeutic option, immunotherapy, is also receiving attention with the successful reduction in allergic symptoms after consistent treatments (Frew). While more research is encouraged, preventative strategies such as early exposure to food allergens and allergen avoidance have emerged as key areas of focus in allergy research (“Overview: Allergies”; Trogen et al.).

However, even though allergies have a lot more to be uncovered, research on allergies is not as focused as it is on more recently discovered illnesses like COVID-19. While encouraging current researchers in the health field to provide innovative, effective treatments with minimized side effects, ordinary people should also recognize the severity of allergies and participate in helping the world for allergy patients. We can help improve allergy patients by reducing pollution through simple tasks like reducing plastic use or encouraging carpools to minimize the release of harmful byproducts in our environment. Through these efforts, we can only hope allergy patients worldwide receive the help they need.

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