Review

Why do allergies occur?

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Abstract

What are allergies and why do they occur? The science underpinning allergies is complex, as are the theories attempting to explain its causes. In this review, I explore the interaction between our decreasing vitamin D levels, our increased cleanliness, and the decreased biodiversity of the human microbiota in destabilising our immunoregulatory systems. These factors are linked to recent lifestyle changes, which helps demystify the increasing rates of atopy in the West. Importantly, I have also illustrated the molecular sequence of events during an allergic reaction and why some allergies are more common than others.

Abbreviations

APC – Antigen Presenting Cell
IgE – Immunoglobulin E
IID – Infectious intestinal diseases
MHC – Major Histocompatibility Complex
OF – Old Friends
Tregs – Regulatory T cells

Introduction and rationale

An allergy is a complex immunoregulatory response occurring after an atopic individual, someone who is predisposed to react in the following way, produces elevated amounts of Immunoglobulin E (IgE) against a typically harmless substance. This is classed as a hypersensitivity type 1 reaction.[1]

Allergies are increasingly common with a staggering 44% of British adults now suffering from at least one allergy, rising by 2 million between 2008 and 2009 alone.[2] Intriguingly, the cases of allergies are specifically increasing in Western countries[3] as the prevalence of food allergies in preschool children is now as high as 10% in Western countries, but remains just 2% in China.[4]

A growing uncertainty as to why allergies occur and why their numbers are rising means that demystifying allergies is increasingly crucial to the world's health and economy.

Main findings

How does an allergic reaction arise?

The first time an atopic individual is exposed to an allergen, the specific allergen protein binds to dendritic cells, which are Antigen-Presenting Cells (APC)[1] which will then hydrolyse the allergen and display them on their MHC II (major histocompatibility complex) surface proteins. A naive CD4+ T-Helper cell binds to this and is activated, it therefore stimulates a strong Th-2 response[3] which will secrete interleukins IL-4 and IL-13 to stimulate B cells. Consequently, the B cells will proliferate and produce antibody-secreting cells, which will produce IgE, and memory cells, explaining why allergies remain for years.[1]

Some of this IgE will bind to the allergen to form an antigen-antibody complex to aid detection and phagocytosis via opsonisation.[3] However, most of the IgE will bind to Fc receptors on Mast Cells, subsequently releasing histamine from cytoplasmic granules to produce the characteristic symptoms of allergic reactions.[1] However, these symptoms will not be noticeable until the individual is re-exposed to the allergen.[3] This process is called sensitisation.[1]

When this atopic individual is then re-exposed to the allergen, the allergen binds directly to the IgE on the mast cells and causes a cross-link of receptors, meaning that both antigen-linking features of an antibody bind to the antigen and so the antibody is now linking two antigens.[3] Consequently, the mast cells degranulate and release a large volume of histamine and other chemicals.[1] Histamine causes vasodilation of blood vessels and renders the capillaries more permeable to white blood cells to allow them to engage with the allergen in the infected tissue, enhancing inflammation.[3] Other symptoms include mild irritations, redness and rhinorrhoea due to excessive mucus production.[1]

The interleukin IL-5 initiates and maintains the inflammation built up by eosinophil white blood cells and releases prostaglandins E1 and E2 to liberate an inhibitor of histamine release, maintaining inflammation.[2] However, this histamine release can also lead to a narrowing of the bronchioles in the lungs – anaphylaxis – which could result in heart failure or even death.[1] The severity of the symptoms depends on the genetic makeup of the individual and the quantity of the allergen consumed.

What can cause an allergic reaction?

A wide range of allergens could cause this allergic reaction explored above. We know of 400 proteins from 170 different foods that act as allergens.[3] Having said this, recent research has found that eight foods (the "Big 8") account for 90% of all food allergies consisting of: milk, eggs, fish, crustacean, shellfish, tree nuts, peanuts, wheat and soybeans.[4] The high prevalence of these eight allergens is often conflated to our large level of consumption of these foods or the structure of the proteins.

Additionally, due to the similarity between the molecular structure of these allergens, 48% of atopic individuals have more than one allergy.[5] This is called cross reactivity. Furthermore, most allergies are due to aeroallergens such as pollens or spores[6] leading to allergic rhinitis (hay fever) affecting around one in every five people in the UK.[8]

Why do allergies occur and why are they now more prevalent?

Answering these questions has given birth to many different theories.

One interesting connection is that our decreasing levels of vitamin D could be detrimental to the immune system and has increased the levels of asthma.[7] An early correction of vitamin D deficiency might maintain a healthy microbial ecology and allergen tolerance, decreasing the risk of food allergies in children.[8] In the US, vitamin D insufficiency has almost doubled in a span of 10 years,[9] while the percentage of atopic individuals is approaching 50% globally.[10] A low level of vitamin D at age six was also associated with increased allergies and asthma at age 14 in one study from Australia.[8] In addition to this, a study involving 616 Costa Rican children with asthma aged 6–14 years, found that 28% of the children had insufficient vitamin D levels.[11]

Most importantly, vitamin D has immunomodulatory effects on allergen-induced inflammatory pathways[12] by acting on the VDR (vitamin D receptor) expressed on a variety of fundamental immune cells, including T cells and B cells.[13] Many of these cells, such as activated macrophages and dendritic cells, are capable of synthesising biologically active vitamin D. This mechanism, called extrarenal expression of CP27B, enables immune cells to quickly increase the local concentration of vitamin D, which is potentially needed to shape adaptive immune responses.[14] A clinical study involving mild allergic asthmatics who underwent an allergen challenge showed a significant increase in vitamin D receptor binding protein (VDBP) but not 24 hours after the allergen challenge. This strongly suggests a role for vitamin D mediated immune responses during the immediate allergic reaction.[15]

The main significance of vitamin D is its ability to inhibit both Th1- and Th2-type responses by having potent antiproliferative effects on CD4+ T cells, suppressing both the production of IL-4 and IL-13 which prevents B cells from being stimulated.[16] Moreover, Regulatory T cells (Tregs) are T-helper cells that play an important role in maintaining immune homeostasis in response to allergen exposure by suppressing Th2 mediated inflammation.[17] Vitamin D can induce antigen specific IL-10–producing Tregs.[17]

This all illustrates the importance of vitamin D in the immune system which could corroborate the claim that it is our decreasing vitamin D levels increasing the number of atopic individuals, as an allergy is just a malfunction of the immune system. Moreover, it also explains that the specifically large increase in allergies in the West could be due to the increased time spent indoors in these wealthy nations and the naturally colder and less sunny climate.[34,35]

However, this theory does not explain why Finland has a higher rate of allergic individuals than the neighbouring Karelian region, despite both regions having the same level of sun exposure.[18] Therefore, it can be concluded that our decreasing vitamin D levels might only be somewhat related to our increasing number of allergies.

One of the more major theories is called the "Hygiene Hypothesis," which proposes that our reduced exposure to microbes due to our increased levels of hygiene and cleanliness has been detrimental to the immune system and has led to this hypersensitivity. These microbes and pathogens would have been important in balancing and developing the immune system.[3]

This theory was not directly based on observations of the immune system but more on relationships between data. This theory was thought to have explained why children who went to day-care had lower instances of allergies than those children who did not attend such a scheme[6] and the fact that farmers' children who drank unpasteurised milk had lower instances of allergies than those who drank pasteurised milk also corroborates the theory.[6] An inverse association between atopy and family size is also explained by this theory as an increased family size would mean increased levels of contact with other individuals, increasing virus exposure and so supposedly reducing atopy because of a more developed and balanced immune system.[19]

The "Hygiene Hypothesis" attempts to explain the European positive correlation between gross national product and incidence of asthma.[20]

However, this theory has led to many dangerous ideas being held by the public such as that we should wash our hands sometimes, but not others. This would increase our rate of infections and the subsequent deaths and reduction in public well-being is a far larger problem than allergies. For example: a recent study has shown that there are 17 million cases a year of food and non-foodborne infectious intestinal diseases (IID) in the United Kingdom, with an annual cost of £1.5 billion to cover resource and welfare losses.[21] Despite hospitals in developed countries adhering to strict hygiene protocols, 7% of inpatients contract an infection.[22] Considering most of these viral infections cannot be treated by antibiotics, preventative methods based on hygiene are crucial. Effective hygiene practices must therefore not be abandoned.

Moreover, the link between infectious diseases and allergies remains controversial as studies carried out in Denmark, UK and Finland reaffirm that allergies are not prevented by childhood infections.[23] Furthermore, it could seem implausible to conflate the major increase in asthma prevalence from the 1960s to the significant changes in sanitation in the 1920s.[24] Reducing our "excessive" hygiene will therefore not necessarily reduce atopy, exacerbating the danger brought by increasing our exposure to infections.

Although scientists agree on some of the fundamentals of the Hygiene Hypothesis, the name of the theory has been considered to be a dangerous misnomer which could potentially suggest the misinformed public to adopt less hygienic practises. The name "Microbial Deprivation Hypothesis" has been suggested as a reform. Avoiding the term 'hygiene' would help focus attention on determining the true impact of microbes on atopic diseases, while minimising the risks of discouraging good hygiene practice.

Furthermore, there has been a consensus among scientists and immune biologists that there are in fact principles within the Hygiene Hypothesis narrative itself that need reform. This has given birth to the "Old Friend Mechanism" theory, first proposed by Professor Graham

A.W. Rook in 2003,[25] which blames the increase in atopy on our less diverse microbiome, which arose from changes in our lifestyle.

The human gut is the natural niche for more than 1014 bacteria of more than 1000 different species,[26] this microbiome is essential in immuno-regulation.[26]

The Hygiene Hypothesis suggested that childhood viral infections are fundamental to the development of the immune system but advancements in evolutionary sciences have proven this as improbable.[25] It is unlikely crowd infections persisted in small hunter-gatherer circles as they either induced immunity or killed the entire group.[27] The Old Friends Mechanism theory proposes that the vital microbial exposures necessary for the development of the immune system are not these colds or other childhood infections, but rather microbes already present during primate evolution when the human immune system was evolving. These microbes are referred to as the "Old Friends" (OF).

OF microbes include species in all environments and the non-harmful microbes transmitted between humans.[25] The species constituting the human OF have varied through time, for example prior to contemporary medical developments it included helminths and hepatitis as these infections survived within hunter-gatherer groups and hence had to be tolerated.[25]

Crucially, these OF exposures interact with the immunoregulatory systems that avoid overreactions, which is the underlying cause of allergies.[28] The diversity of microbial exposure is fundamental for two main reasons. Firstly, a wide variety of organisms would be tolerated by infants if they are exposed to a wide variety of nom-harmful bacteria during these crucial years where immunoregulatory systems are being established. Secondly, increasing the variety of bacteria that one is exposed to establishes memory lymphocytes to recognise novel pathogens.[29]

It is agreed that the most vital times for OF exposure are during pregnancy, delivery and the early stages infancy.[29] However, the nature of these stages in our lives are drastically changing, which changes our microbial exposure and so leads to the reduction of the biodiversity of the human microbiome which could therefore lead to the now imbalanced immune system being hypersensitive to certain substances.

For example, Caesareans have increased in prevalence since 1950 and now account for 25% of UK births[30] and a 2008 review showed that a Caesarean section is linked to an increased risk of atopy.[31] Even breastfeeding compared to bottle feeding has a large influence on gut microbiome.[32]

In addition to this, Finnish research concluded that people living in rural spaces had a more biodiverse skin microbiota and a reduced rate of atopy.[33] However, about 82% of people in England now live in urban areas,[34] which decreases the biodiversity of the microbiota, possibly explaining the sharp rise in allergies. This is exacerbated by the fact that about 50% of people spend less than one hour a day outdoors, according to a survey across the US and Europe with a sample size of nearly 17,000 adults.[35]

Furthermore, our diet can influence the health and diversity of our microbiota.[36] It has been reported that a diverse diet which is high in fibre and polysaccharides, which are digested by the microbiota,[37] is the most effective in maintaining the health of our microbiota.[37] Whereas a diet that lacks in fibre can eliminate crucial microbes.[38] Although researchers at the University of Otago in New Zealand say people should be eating a minimum of 25g of fibre per day, fewer than one in 10 adults eats 30g of fibre daily in the UK.[39] This has led to the unfortunate fact that people living in developed countries have a less diverse microbiota than hunter-gatherers[40] which could have led to the large number of atopic individuals in these countries.

Another lifestyle alteration which has reduced the biodiversity of the human microbiome could have been the increase in prescribed antibiotics after their development in the 1950s, aligning with the increase in allergies since the 1970s.[41] According to recent studies, antibiotics, especially macrolides, can enhance the risk of asthma in children by inducing long-term effects on the microbiota.[42] This notion was supported by a 2014 review of over 50 studies.[42]

Our vitamin D intake, as explored previously, is also connected to the OF mechanism theory as it has recently been shown that the composition of the gut microbiome can be altered by vitamin D exposure.[43]

However, it could be argued that all these trends could also be explained using the Hygiene Hypothesis as both the Hygiene Hypothesis and Old Friend mechanism theories could be seen to be arguing based on the same principle. Both the reducing level of exposure to microbes and infectious diseases, proposed by the Hygiene Hypothesis, and the reducing biodiversity of the human microbiome from reducing microbial exposure, proposed by OF theory, are causative of the same problem and could be seen as synonymous as both appear to intertwine.

However, further analysis of the validity of the Hygiene Hypothesis claim magnifies the subtle difference between the two theories and exemplifies the higher credibility of the OF mechanism theory.

It appears invalid to claim that our decreased exposure to infectious diseases could have increased the atopy rate, possibly by causing the decline in the biodiversity of the microbiome, as the simple premise that "we are too clean" is invalid. It has been proven that implementing regular anti-bacterial cleaning habits in Western homes has no long-term effects on the levels of microbes[10] as they are replaced by dust and air.[44] Excessive cleanliness therefore does not facilitate a completely sterile home.

The most important point is that since the 1800s, the microbial content of our homes has significantly changed. Cleanliness practices are not solely to blame for this, the adjustment from rural surroundings in the 1800s to our modern indoor-dominated life has played a huge role.[25] This means that we now interact with a totally different and less diverse mix of microbes. It is this change that is most likely the cause of the increase in atopy, rather than our increased cleanliness and reduced infections.

There are also other factors that argue against the role of hygiene in increasing atopy. Hygiene is insignificant in causing microbiome disruption compared to our changed diet and the increase in antibiotic use.[25] Additionally, exposure to the natural environment facilitates the interaction, via the airways, with the microbes found in house dust. Hygienic practices are unlikely to be responsible for the reduced inputs from this key source.

Despite the Old Friends mechanism being a preferable theory over the Hygiene Hypothesis, the reduced focus on easily improvable factors such as hygiene and cleanliness does mean that acting based on the Old Friends mechanism is less feasible.

Allergies and their increase are most likely explained by the increasingly profound reduction of the biodiversity of the human microbiome due to changes to our daily lives (as proposed by the OF mechanism theory) and, to a limited extent, our excessive cleanliness (as proposed by the Hygiene Hypothesis). Additionally, our decreasing vitamin D levels could contribute to these changes to our human microbiome, all causing this malfunction of the immune system.

Conclusions and recommendations

We now understand that allergies are most likely to be explained by a genetic tendency interacting with our less biodiverse microbiome,

which is because of many factors. These factors include our reduced interaction with nature and possibly our reduced exposure to pathogens or our decreased levels of vitamin D, to cause the immune system to "malfunction" and treat what is harmless as if it were harmful. Based upon this crucial understanding, we can approach solving atopy by attempting to increase our microbial exposure by altering our diets or even conducting microbiota transplants in C-section infants.

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