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Fungal Proteases in the Preventative Treatment of Peanut Allergies: A Research Protocol

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Abstract

Peanut allergies are a common autoimmune disorder that impacts millions of people worldwide. Currently, there are no known treatments to prevent allergic reactions to peanuts besides avoiding the allergen. To combat this, previous studies have found that fungal proteases can prevent an allergic response; the fungal proteases bind a peanut-specific IgE immunoglobulin, blocking the allergic response. We propose to orally administer these previously identified fungal proteases isolated from the fungus *Aspergillus Niger* before exposure to peanut antigens. If the fungal proteases successfully bind the peanut-specific IgE before exposure, peanut allergenicity will be reduced. To test our experimental drug, we will utilize peanut-sensitized mice strains, with one control group receiving a placebo and two treatment groups receiving either a high dose of 2.5mg or regular dose of 1.25mg of the drug. All three groups will then be exposed to the peanut allergen, and allergy responses will be monitored through body temperature measurements, blood histamine tests and enzyme-linked immunosorbent assay (ELISA) testing the presence of peanut-specific IgE. We anticipate that the fungal proteases will prevent all allergic reaction responses from occurring such that body temperature will remain stable, blood histamine levels will not increase, and the presence of peanut-specific IgE will be lessened. This novel oral drug will be used as a pre-exposure preventative treatment, unlike the current post-exposure treatments, such as an Epi-pen, filling a key gap in knowledge of preventative treatment for peanut allergies.

Keywords: fungal proteases; peanut; autoimmune disease; aspergillopepsin; allergenicity; immunoglobulin E binding; ELISA

Introduction

Food allergies are immune reactions to proteins in food that produce negative clinical symptoms, manifesting as respiratory, dermatological, and gastrointestinal symptoms [1]. Peanut allergies (PA) are among the most reported and severe kinds of food allergies seen in individuals [2, 3]. PAs are an immunoglobulin E (IgE) mediated type 1 hypersensitivity and occur when an individual ingests or comes into contact with a protein in peanuts known as an allergen. In response, the body produces IgE, which binds to high-affinity IgE receptors on basophils and mast cells [4, 5]. Once activated, these cells release mediators called histamines, which cause the rapid onset of allergy symptoms [6]. These symptoms include nasal congestion, urticaria and respiratory problems [7]. Severe, anaphylactic reactions can result in life-threatening circulatory and respiratory complications [7]. The early phase of the allergic reaction is characterized by sneezing and itching, which ultimately progresses into nasal congestion [8, 9]. These symptoms can persist for hours after the initial exposure to the allergen as histamine plays a role in both the early and late phases of the allergic reaction [8]. Specifically, mast cell-mediated histamine release is the source for the early phase of the allergic reaction and causes immediate reactions lasting up to 2 hours [8, 9]. While basophil-mediated histamine release is the source of late-phase allergic reactions and typically occurs 4-12 hours after the initial reaction and can last up to 73 hours [8, 9].

Currently, the recommendations for managing a PA are peanut avoidance and carrying Epi-pens in case of a reaction [1]. Epi-pens deliver a dose of epinephrine, which alleviates the symptoms of an already occurring allergic reaction. Epinephrine constricts blood vessels, causing an increase in blood pressure if it had fallen during the reaction, and reduces urticaria [10]. Epinephrine does this by activating alpha-adrenergic receptors in vascular tissue [10]. It also relieves the associated respiratory symptoms by stimulating bronchodilation, allowing the muscles in the lungs to relax [10, 11]. However, despite its ability to stop allergic reactions, injecting epinephrine can also cause adverse effects in many of the body's visceral systems [12]. As a result, epinephrine usage has been found to cause

dyspnea, tremors, dizziness, vomiting, hypertension, vasospasm and other harmful side effects in some patients [12]. Therefore, an alternative to the current standard of treatment is required to reduce the risk of PA. To do this, an alternative form of treatment must break down or alter the allergens in peanuts to avoid a reaction [3]. Recent literature has suggested the potential of using fungal proteases to break down these allergens in peanuts to reduce allergic reactions in individuals [13].

An article by DeFreece et al. (2020) evaluated the effects of using fungal proteases from the fungi *Aspergillus Niger* to identify secreted proteins that may be useful as future food allergen processing enzymes [13]. Utilizing immunoblotting and competitive ELISA, their findings indicated that one of these secreted proteins, Aspergillopepsin from *Aspergillus Niger*, was successful in cashew protein degradation which reduced antibody binding to cashew allergens [13]. Immunoblotting procedures treated 10µg of cashew extract samples with 5 µg of Aspergillopepsin for digestion [13]. They monitored the extracts for 90 minutes to quantify rabbit IgG binding to cashew nut allergens [13]. After 30 minutes, IgG binding significantly reduced to less than 5%, suggesting that Aspergillopepsin effectively degraded the cashew nut allergens [13]. Additionally, competitive ELISA assays were used to assess whether Aspergillopesin-treated cashew extracts would reduce IgE binding of cashew allergens under gastric-like conditions [13]. The assay incubated 25 µL of treated cashew nut extracts, 25µL of pooled sera from eight cashew-allergic patients, and 50 µL of Tris-glycerine, which was added to 1 µg of the cashew nut sample for two hours [13]. The results demonstrated that Aspergillopepsin-treated cashew nut extracts exhibited reduced IgE binding compared to the untreated extracts [13]. This is significant as IgE binding triggers allergic reactions. By reducing this binding, researchers were able to decrease the risk of allergic response under gastric-like conditions. As a result, the authors recommended using Aspergillopepsin in food processing procedures to reduce the allergenicity associated with cashews [13]. These findings from DeFreece et al. suggest that Aspergillopepsin could break down similar protein structures found in other nuts like peanuts [13]. Since peanuts and cashews share similar protein families, like vicilin and legumin, there is potential for Aspergillopepsin to also degrade peanut proteins and reduce their allergenicity [14, 15]. Peanuts and cashews have been found to share similar IgE epitopes which could explain why individuals with PAs also experience allergic reactions to tree nuts like cashews [14,15]. Due to these similarities and cross-reactivity, future research should explore Aspergillopepsin as a potential preventative treatment for PA.

Furthermore, rather than relying solely on Aspergillopepsin during food processing procedures, a preventative oral pill containing this enzyme should be investigated to reduce the allergenicity of peanuts. This preventative pill could offer a more convenient and targeted approach for those affected by PAs to better manage their allergies and enhance their quality of life. This paper will assess the efficacy of taking oral pills containing Aspergillopepsin before consuming peanuts to lessen allergic reactions in mice. If the fungal protease, Aspergillopepsin, successfully binds to and degrades the peanut allergen, there will be a reduction in the peanut-specific IgE immunoglobulin binding after being exposed to the peanut allergen, and a subsequent allergic reaction will not occur.

Methods

We plan on using the mature (6-week-old) CC027/CeniUnc strain of Mus musculus mice that have been sensitized to peanuts by genetically modifying them, which increases their gut permeability and decreases immunoglobulin A (IgA) production, eliciting peanut sensitivity.[16]. Increasing gut permeability contributes to causing peanut sensitivity in the mice by allowing a greater number of allergens across the intestinal lumen and increasing interactions with the immune system [17]. This mouse model will be used without an adjuvant as the models have shown peanut sensitivity on their own [18].

To ensure the mice are allergic to peanuts, we will perform an IgE immunoglobulin quantification via an ELISA serology test specific to the peanut antigen. A value of 0.70 kU/L or greater of IgE indicates an allergic response [19]. To confirm that the mice were sensitized, 2.5mg of peanuts will be orally administered to induce an allergic reaction to confirm their sensitivity to peanuts [20]. If IgE production specific to peanuts is induced, it will show that the mice are allergic to peanuts, and a reaction will occur [21, 22].

We will utilize a commercially available preparation of the Aspergillopepsin protease in the experimental groups [13]. To test the efficacy of the Aspergillopepsin protease, we will use two experimental groups and two control groups. Each group will contain an equal number of male and female mice to account for possible sex-specific interactions with the Aspergillopepsin protease. The active and placebo administration will be via oral administration, and the peanut allergen will be orally administered. One control group (negative control) will receive a saline placebo dosage to establish whether an allergic reaction occurs when the mice are administered peanuts. The other control group (positive control) will be administered the active Aspergillopepsin protease but will not be exposed to peanuts. The two experimental groups will receive the Aspergillopepsin protease, with one high-dose group and one regular-dose group. The higher dosage for the Aspergillopepsin protease will be 2mg, and the regular dosage will be 1.25mg. These dosages were determined based off previous studies, where 2.5mg of peanut extract elicited an anaphylaxis response and a 2:1 ratio of peanuts to Aspergillopepsin was previously shown to be effective in

preventing such allergic response [13, 23]. A regular and a higher dosage are utilized to determine if there is a difference between the amount of Aspergillopepsin compared to the amount of peanut allergen. The saline placebo administered will also be 2mg to reduce confounders. The peanut allergen is administered at varying time points after the administration of the Aspergillopepsin protease to test whether the time the peanuts were given impacts how effective the protease is at stopping an allergic reaction [13]. Additionally, administering at different time points ensures we do not discount the possible confounding variable of time, whether the time when the protease is administered impacts the effectivity. The time points used will be immediately after protease administration, 10 minutes after, 20 minutes after and 40 and 60 minutes after. Specifically, these time points were chosen as Aspergillopepsin becomes less than 10% effective after 60 minutes of exposure to the acidic environment of the digestive system [24]. These time points allow us to determine how long the optimal timing between protease administration and peanut allergen exposure.

To test if an allergic reaction is happening, we will observe the mice and note any anaphylactic symptoms they experience by measuring their body temperatures; a decrease in temperature greater than 0.5°C means an allergic reaction is occurring [25]. We will also measure the IgE quantification via ELISA serology test to determine IgE presence specific to peanuts and histamine presence in blood via blood tests [26, 27]. The blood for the histamine test will be collected from the saphenous vein on the back of the thighs of the mice [28]. Using this site allows for taking up to four samples of 0.2 mL each. There will be 4 samples taken at each of the time points mentioned above: 10 minutes, 20 minutes, 40 minutes, and 60 minutes after protease administration. Histamine presence is measured during an allergic reaction, such as when histamine is released and mediates an immune response to the allergen [26]. Histamine increases of greater than 10 nmol/L indicate an allergic reaction occurring in the mice [29]. To remove a possible confounding variable, we will keep the mice in a temperature-regulated room. Given that we are measuring their body temperature to detect anaphylaxis, we need to keep the room temperature standard.

The success of the Aspergillopepsin protease treatment will be evaluated through an analysis of variance (ANOVA) statistical test analyzing the data on body temperature, quantity of immunoglobulin, and amount of histamine present from the four groups: regular dose, high dose, placebo, and protease only. The ANOVA test will compare the means for each of these groups for each parameter. The null hypothesis for an ANOVA test assumes no difference between the means, indicating that there is no change due to the treatment [30, 31]. The alternative hypothesis suggests statistically significant differences between at least two of the group's mean. The F-statistic and the associated p-value are used to determine whether the difference is statistically significant or not. The F-statistic represents a ratio of two mean square values. If the p-value corresponding to the F-statistic is less than 0.05, the null hypothesis is rejected as the difference between the means is statistically significant. If the corresponding p-value is greater than 0.05, the difference between the means is insignificant, and thus, the null hypothesis is accepted [30, 31]. One drawback of using the ANOVA statistical test is the ANOVA only determines if there is a difference between at least two groups, it does not specify which groups have significant differences. A post hoc test is conducted to pinpoint the groups that display statistically significant differences.

Results

40 mice will be utilized in the experiment with an equal number of male and female sex mice in each group.

Anticipated Results

If the fungal protease, Aspergillopepsin, successfully binds and degrades the peanut allergen, there will be a reduction in the peanut-specific IgE immunoglobulin binding after being exposed to the peanut allergen, and a subsequent allergic reaction will not occur [19]. Levels of IgE greater than 0.70 kU/L suggest that an allergic reaction is occurring, while levels below 0.10 kU/L indicate that no allergic reaction is present [19]. Therefore, IgE levels lower than 0.10 kU/L would be expected for the group that receives the fungal protease treatment. These results would support the hypothesis that the fungal protease Aspergillopepsin can successfully prevent an allergic reaction.

Discussion

Peanut allergies pose a significant and increasing health risk [2]. Current treatments primarily focus on managing the individual's symptoms after exposure to the allergen. The leading preventative treatments rely heavily on avoiding the allergen, which can be incredibly challenging. This research focuses on investigating the use of fungal proteases to prevent allergic reactions. This treatment involves using fungal proteases to block the binding of IgE and thus disrupt the immune response that leads to an allergic reaction [13]. By impeding the IgE binding, the fungal proteases pre-emptively prevent allergic reactions to peanuts. This research prioritizes prevention over the retroactive treatment of allergic reactions and, by doing so, aims to improve the quality of life for individuals with peanut allergies. Utilizing multiple parameters to assess the efficacy of the fungal protease Aspergillopepsin as a treatment for peanut allergies enhances the reliability of the conclusions that will be reached. Future research should explore whether this protease interacts with other medications or foods, a focus that is beyond the scope of the current study. This would provide a more comprehensive understanding of the

protease's potential interactions and safety in various contexts. A limitation of the study is the generalizability as the results obtained from using a mouse model may not be an entirely accurate predictor of how the protease treatment will act in humans.

Conclusions

We aim to uncover whether fungal proteases can be used as a pre-exposure preventative treatment for peanut allergies. The fungal proteases isolated from *Aspergillus Niger* would bind peanut-specific IgE immunoglobulin and block an immune response from occurring [3]. We anticipate that the fungal proteases will successfully stop an allergic reaction in both the regular- and high-dosage groups. Thus, the mice's body temperature will remain stable, the blood histamine levels will not increase, and the presence of IgE will not be found. For these parameters, both the ANOVA and post hoc tests should show a significant difference between the means for the control group and the low- and high-dosage groups. Future directions for this study could be to test the efficacy of the Aspergillopepsin protease on other nuts that are a common cause of food allergies. This research will be a step forward in identifying and implementing a preventive pre-exposure treatment for peanut allergies and other nut allergies including walnuts, almonds, pecans and cashews. This will allow those impacted by the autoimmune disorder to not worry about avoiding peanuts and possibly allow them to intentionally consume peanuts, improving their quality of life and easing any stress associated with food allergies.

List of Abbreviations Used

ELISA: enzyme-linked immunosorbent assay
PA: peanut allergy
IgE: immunoglobulin E
IgA: immunoglobulin A
ANOVA: analysis of variance

Conflicts of Interest

Maggie Mallabone, Norah Dickie, and Portia Viel declare that they have no conflict of interests.

Ethics Approval and Participant Consent

Our study will require ethics approval from the Queen's University Animal Care Committee (UACC) to ensure the proper and ethical treatment of the mice. Considerations include limiting the number of mice used in the trial, ensuring standardized treatment of the mice, and ensuring that the significance of the research justifies the usage of animals. Our study does not require participant consent as humans are not involved.

Authors' Contributions

MM: Contributed to the study design, drafted, and revised the manuscript, and gave final approval of the manuscript.
ND: Made contributions to the design of the study, drafted, and revised the manuscript and gave final approval of the manuscript.
PV: Made contributions to the study design, drafted, and revised the manuscript and gave final approval of the manuscript.

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