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Groundbreaking Discoveries in Immunology

Title: Drug-induced IgG-neutrophil-mediated anaphylaxis in humans: uncovered!

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Seminal work by Oettgen *et al.*¹ in the early 90's revealed the existence of alternative pathways of anaphylaxis (non IgE-mediated) in IgE-deficient mice. These are mediated by IgG-immune complexes which, depending on their nature, signal on a number of myeloid cells including macrophages/monocytes, basophils, mast cells and neutrophils. While extensively characterized in mice, conclusive evidence of the existence of alternative pathways of anaphylaxis in humans have remained elusive. This is partly due to the rarity of these complex reactions, and the scarcity of biomarkers to identify them as well as experimental systems to tease apart their contribution from that of the classical pathway (IgE-mediated)².

The recent work by Bruhn's group³ investigated acute hypersensitivity reactions (AHR) to drugs in a cohort of patients suspected to be allergic. They provide strong, non-causal evidence of the contribution of a human alternative pathway in drug-induced anaphylaxis. Their findings were substantiated in patients undergoing general anesthesia whom received, intravenously, neuromuscular-blocking agents (NMBAs).

NMBA-specific IgG levels, activation of Fc γ receptors and neutrophils (degranulation and NETosis) and PAF-acetylhydrolase activity (a surrogate of PAF release) were correlated with anaphylaxis severity. Additionally, *ex vivo* experiments demonstrated the ability of human NBMA-specific IgG to induce neutrophil activation in the presence of NMBA.

A clinical implication of this study is that serum levels of NMBA-specific IgG may facilitate the identification of patients at risk of developing anaphylaxis on systemic administration of NMBA. Furthermore, this pathway might contribute to severe hypersensitivity reactions in similar clinical settings where large amounts of antigen such as protamine, dextran, aprotinin, *etc.* are administered systemically. Along this line, this pathway may worsen food-induced anaphylaxis if a sufficient amount of allergen were to be absorbed into the systemic circulation of allergic individuals.

The size of NMBA (<1kDa) precludes antibody recognition. Thus, NMBA binding to a carrier is critical to enable antibody detection. In this regard, the haptenization process and the identity of the human proteins that bind NMBA needs to be ascertained. Lastly, the contribution of each IgG subclass to this pathway is not known. It is presumable that some IgG subclasses exert a regulatory role while others drive anaphylaxis. Hence, investigating their function in NMBA-mediated anaphylaxis will extend the knowledge of this pathway and improve the ability to predict individuals at risk.

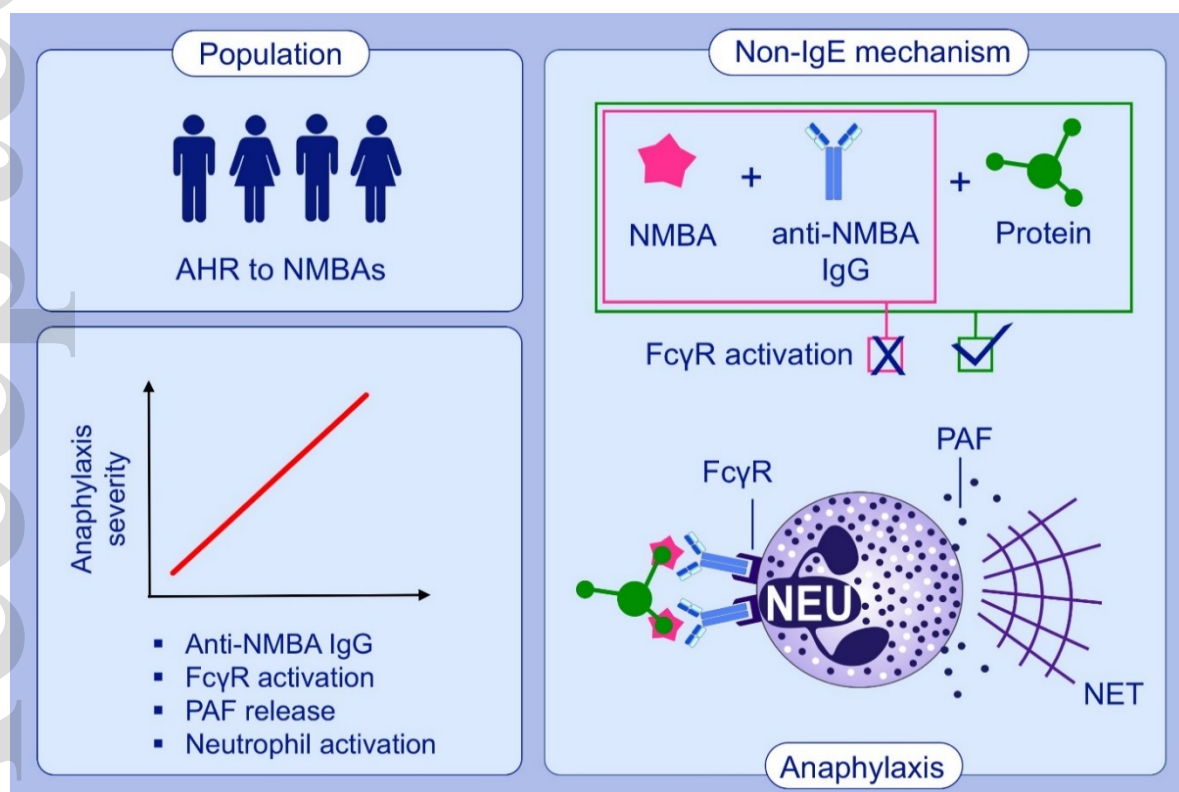


Figure 1. An alternative pathway (IgG-neutrophils) of anaphylaxis contributes to human drug-mediated acute hypersensitivity reactions (AHR). AHR to neuromuscular-blocking agents (NMBAs) were investigated in a cohort of patients suspected to be allergic. Serum levels of NMBA-specific IgG, activation of Fc γ receptors (Fc γ R) and neutrophils, and production of platelet-activating factor (PAF, indirectly measured as PAF-acetylhydrolase activity) were correlated with anaphylaxis severity. Haptenization of NMBA enables NMBA-IgG immune complex formation and Fc γ R signalling on neutrophils that induces degranulation and extracellular trap formation (NET).

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References

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