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REVIEW ARTICLE

Historical Anecdotes and Breakthroughs of Histamine: From Discovery to Date

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Abstract: ***Aim:*** Investigating about the history of allergies and discovery of the histamine's role in the immune response through historical references, starting with ancient anecdotes, analysing the first immunization attempts on animals to understand its importance as the anaphylaxis mediator. Moreover, we shortly resume the most recent discoveries on mast cell role in allergic diseases throughout the latest updates on its antibody-independent receptors.

Methods: Publications, including reviews, treatment guidelines, historical and medical books, on the topic of interest were found on Medline, PubMed, Web of Knowledge, Web of Science, Google Scholar, Elsevier's (EMBASE.comvarious internet museum archives. Texts from the National Library of Greece (Stavros Niarchos Foundation), from the School of Health Sciences of the National and Kapodistrian University of Athens (Greece). We selected key articles which could provide ahistorical and scientific insight into histamine molecule and its mechanism of action's discovery starting with Egyptian, Greek and Chinese antiquity to end with the more recent pharmacological and molecular discoveries.

Results: Allergic diseases were described by medicine since ancient times, without exactly understanding the physio-pathologic mechanisms of immuno-mediated reactions and of their most important biochemical mediator, histamine. Researches on histamine and allergic mechanisms started at the beginning of the 20th century with the first experimental observations on animals of anaphylactic reactions. Histamine was then identified as their major mediator of many allergic diseases and anaphylaxis, but also of several physiologic body's functions, and its four receptors were characterized. Modern researches focus their attention on the fundamental role of the antibody-independent receptors of mast cells in allergic mechanisms, such as MRGPRX2, ADGRE2 and IL-33 receptor.

Conclusion: New research should investigate how to modulate immunity cells activity in order to better investigate possible multi-target therapies for host's benefits in preclinical and clinical studies on allergic diseases in which mast cells play a major role.

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1. INTRODUCTION

Histamine, or 2-(1H-Imidazol-4-yl)-ethanamine (IUPAC), is an aminergic neurotransmitter and plays several important roles in the regulation of physiological and pathological processes. It is an organic nitrogenous compound generated from the decarboxylation of the aminoacid histidine, a reaction catalysed by the enzyme L-histidine decarboxylase. It is an important biochemical mediator involved in local and systemic immune responses against allergens, but is an important molecule in the inflammatory response, where it increases the permeability of the capillaries to allow immune system and some blood proteins to destroy pathogens. Tissutal histamine is contained in the mast-cells granules, instead most circulating histamine is stored in the basophils and eosinophils granules.

Moreover, histamine is a neurotransmitter involved in important functions of the central nervous system. It is synthetized by neurons located in the tubero-mammillary nucleus of the posterior hypothalamus, which project diffusely to most cerebral areas. They control several functions, such as sleep/wakefulness, thermoregulation, hormonal secretion, food intake and memory. Finally, histamine regulates many functions of gastrointestinal system: ECL (enterochromaffin-like cells) located in stomach regulate gastric secretion via histamine release after stimulation with gastrin [1, 2].

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2. HISTORICAL PERSPECTIVE OF ALLERGIC DISEASES

The term "allergy" appeared for the first time recently, at the very beginning of the 20th century, with the discovery of the phenomenon of "anaphylaxis" and of the main biochemical mediator involved in its pathogenesis, histamine. First historical references about allergies were found in the ancient Chinese medical legends and in the Egyptian society, with the first descriptions of asthma-like symptoms and anaphylactic shock [3, 4].

According to the legend, it was Shen Nong (2.700 b.C.), considered the Father of Chinese Herbal Medicine, who first experimented the *Ephedra sinica*, an evergreen shrub-like plant native to central Asia, known to the Chinese as "*Ma Huang*", to treat asthma-like symptoms, to relieve bronchospasms, produce vasoconstriction, reverse congestion, and inhibit mucus secretion. The *Nei Ching Su Wen*, the world's oldest treatise of internal medicine, described respiratory symptoms which may refer to asthma:

"…Man is afflicted when he cannot rest and when his breathing has a sound (is noisy) or when he cannot rest and his breathing is without any sound. He may rise and rest (his habits of life may be) as of old and his breathing is noisy; he may have his rest and his exercise and his breathing is troubled (wheezing, panting): or he may not get any rest and be unable to walk about and his breathing is troubled. There are those who do not get a rest and those who rest and yet have troubled breathing..." [5 ,6].

Also as concerns Egyptian civilization, many authors agree that Pharaoh Menes died for anaphylactic shock between 3.640 and 3.300 b.C. after he was stung by a hornet or a wasp during a trip to the current Cornish region in U.K. where he went with his troop to find tin to replace the copper of their swords; moreover, a very ancient Egyptian manuscript, the Ebers Papyrus (1.550 b.C.), could represent one of the first document on allergic respiratory symptoms; it was unearthed in Thebes in 1862 and then translated into German in 1873. The Ebers Papyrus was considered a divinely inspired text that contained the worldly knowledge of Thoth, the Egyptian god of learning and the patron of physicians [7-9].

In the Ebers Papyrus, asthma is considered to be a "disorder or foulness" of the ducts that were thought to distribute air and water to the organs, including the lungs. Physicians, therefore, attempted to heal the ducts with grapes, yellow ochre and frankincense. It also described the use of a special apparatus for inhalation:

"…Thou shalt fetch seven stones and heat them by fire, thou shalt take one thereof and place a little of these remedies on it and cover it with a new vessel whose bottom is perforated, and place a stalk of reed in this hole; thou shalt put thy mouth to this stalk so that thou inhalest the smoke of it. Likewise, with all stones..."

Hippocrates of Kos (Ἱπποκράτης ὁ Κῷος, 460−377 b.C.), was a Greek physician of the Classical Greece, who is considered one of the most outstanding figures in the history of medicine and the founder of the Hippocratic School of Medicine. In the "Περί αέρων, τόπων, υδάτων" *(treatise of Airs, Waters, and Places)* he made the first systematic attempt to set forth a causal relationship between human diseases and the environment [10].

He used the term "*idiosyncrasy*" (*ιδιοσυγκρασία*) describing respiratory symptoms that, today, can be related to asthma and eczema, particularly he wrote about a form of asthma which was commonly diffused between tailors, fishermen, metal workers, stonemason and blacksmiths, observing a correlation that today is called "occupational asthma" [11, 12]. He well-described the spasmodic nature of the disease and also observed a strong prevalence in particular climatic conditions. He believed its onset to be caused by moisture, climate and occupation:

".... ἥτις μὲν πόλις πρὸς τὰ πνεύματα κεῖται τὰ θερμά ταῦτα δ' ἐστὶ μεταξὺ τῆς τε χειμερινῆς ἀνατολῆς τοῦ ἡλίου καὶ τῶν δυσμέων τῶν χειμερινῶν καὶ αὐτῇ ταῦτα τὰ πνεύματά ἐστι σύννομα, τῶν δὲ ἀπὸ τῶν ἄρκτων πνευμάτων σκέπη, ἐν ταύτῃ τῇ πόλει ἐστὶ τά τε ὕδατα πολλὰ καὶ ὕφαλα, καὶ ἀνάγκη εἶναι μετέωρα, τοῦ μὲν θέρεος θερμά, τοῦ δὲ χειμῶνος ψυχρά.…τοῖσί τε παιδίοισιν ἐπιπίπτεσπασμούς τε καὶ ἄσθματα καὶ ἃ νομίζουσι τὸ παιδίον ποιεῖν..." [13].

(….a city that is exposed to hot winds - these are between the wintry rising, and the wintry setting of the sun and to which these are peculiar, but which is sheltered from the north winds; in such a city the waters will be plenteous and saltish, and as they run from an elevated source, they are necessarily hot in summer, and cold in winter….infants are subject to attacks of convulsions and asthma, which they consider to be connected with infancy…)

At the same time, he noticed many cases of "food reactions" to dairy products among people living in the same environment. The Hippocratic theory to explain these strange symptoms was that they appeared when one of the body's humours, that he called "*phlegm*" (*φλέγμα*), reached the brain and, throughout the nasopharyngeal cavity, flowed in the lungs. He prescribed as a therapy for this disease purging and bloodletting, which remained the norm for long time. The actual term "asthma" comes from the Greek word for "wind" or "to blow" (*ἄσθμα*).

Another major Greek clinician who deepened the typical respiratory symptoms of an asthmatic attack was Aretaeus of Cappadocia (Ἀρεταῖος ὁ Καππαδόκης, 1st century a.C.). In his treatise "Περί αιτίων και σημείων χρονίων παθών" *(On the causes and symptoms of chronic disease)*, in the second book*, Κεφ. ια'. "περὶ Ἄσθματος" (Chapter XI. On Asthma),* he emphasized the wheezing, difficulty to lying in bed and the dry productive cough as characteristics of the respiratory disease [14-16].

"…εἰ ἀπὸ δρόμου καὶ γυμνασίων καὶ παντὸς ἔργου δυσπνοεῖ ἡ ἀναπνοὴ, ἄσθμα καλεῖται: καὶ ἡ νοῦσος δὲ ὀρθόπνοια, καὶ ἥδε κικλήσκεται ἄσθμα: ἐν γὰρ τοῖσι παροξυσμοῖσι ἀσθμαίνουσι καὶ οἵδε. ὀρθόπνοιαν δὲ ἐκάλεον, οὕνεκεν ὀρθίῳ σχήματι μοῦνον ἀναπνέουσι εὐφόρως: πνὶξ γὰρ ἐν κατακλίσι."

(…if from running, gymnastic exercises, or any other work, the breathing become difficult, it is called *Asthma* (ἄσθμα); and the disease *Orthopnœa* (ὀρθόπνοια) is also called Asthma, for in the paroxysms the patients also pant for breath. The disease is called *Orthopnœa*, because it is only

when in an erect position (**ὀρθίῳ** σχήματι) that they breathe freely; for when reclined there is a sense of suffocation…)

"…πάσχει δὲ πλεύμων: ξυμπαθέει δὲ καὶ τὰ ξυντελοῦντα ἐς ἀναπνοὴν, διάφραγμα, θώρηξ: ἢν δὲ καρδίη πάθῃ, οὔκοτε ἐς πολλὸν διαρκέσειε. τῇδε γὰρ ἡ τῆς ἀναπνοῆς καὶ τῆς ζωῆς ἀρχή. αἰτίη δὲ ψύξις καὶ ὑγρότης τοῦ πνεύματος: ὕλη δὲ ὑγρὰ, [p.74] παχέα, κολλώδεα…" [16].

(…the lungs suffer, and the parts which assist in respiration, namely the diaphragm and thorax, sympathise with them. But if the heart be affected, the patient could not stand out long, for in it is the origin of respiration and of life. The cause is a coldness and humidity of the spirit (*pneuma*); but the *material* is a thick and viscid humour…)

"…εὐπαθέες δὲ γυναῖκες ἀνδρῶν μᾶλλον, ὅτι περ ὑγραί τε καὶ ψυχραί: οἱ δὲ παῖδες τούτων περιγίγνονται Ρ῾ηΐτερον, ἡ γὰρ φύσις ἐν αὐξήσι θερμῆναι δυνατωτάτη. ἄνδρες δὲ εἰ καὶ μὴ Ρ῾ηΐδιοι παθεῖν, ἀλλὰ θνήσκουσι θᾶσσον. ἀμβολὴ δὲ θανάτου ὅσοισι ἐν ἔργου πρήξι, ἢ ἐν εἰρίοισι πλεύμων θάλπεται καὶ διαίθεται, ὁκοῖόν τι τοῖσι τῆς τιτάνου ἐργάτῃσι, ἢ χαλκεῦσι, ἢ σιδηρεῦσι, ἢ καὶ λουτρῶν πυρσευτῆρσι…" [16].

(…women are more subject to the disease than men, because they are humid and cold. Children recover more readily than these, for nature in the increase is very powerful to heat. Men, if they do not readily suffer from the disease, die of it more speedily. There is a postponement of death to those in whom the lungs are warmed and heated in the exercise of their trade, from being wrapped in wool, such as the workers in gypsum, or braziers, or blacksmiths, or the heaters of baths…)

"…Μελλησμοῦ δὲ σημήϊα, βάρος τοῦ θώρηκος, ὄκνος ἐς τὸ ξύνηθες ἔργον, ἀτὰρ ἡδὲ ἐς ἅπασαν πρῆξιν, δύσπνοια ἐν δρόμῳ, ἢ πρὸς ὁδὸν ὀρθήν: βραγχώδεες καὶ βηχώδεες, φῦσα ἐν τοῖσι ὑποχονδρίοισι καὶ ἐρυγαὶ παράλογοι, ἀγρυπνίη, θερμασίη νύκτωρ σμικρὴ, ἀσαφής : Ρ῾ὶς ὀξείη, ἐς ἀναπνοὴν ἑτοίμη. ἢν δὲ ἐπὶ μέζον τὸ κακὸν ἕρπῃ, μῆλα ἐρυθρά: ὀφθαλμοὶ προπετέες, ὡς ἐπ᾽ ἀγχόνῃ, Ρ῾ωγμὸς ἐν ἐγρηγόρσι: πολλὸν δὲ μέζον τὸ κακὸν ἐν ὕπνῳ: ὑγρὴ καὶ ἄηχος ἡ φωνή: πολλοῦ καὶ ψυχροῦ ἠέρος ἐπιθυμίη : ἐς τὸ ὕπαιθρον ἴενται, πᾶς γὰρ αὐτέοισι οἶκος ἐς ἀναπνοὴν οὐ διαρκής : ἀναπνέουσι ὄρθιοι, ὅκως ἅπαντα σπάσαι τὸν ἑλκόμενον ἠέρα ποθέοντες, ὑπ᾽ ἀπορίης δὲ τοῦ ἠέρος καὶ διοίγουσι τὸ στόμα, ὡς τῷδε μέζονι χρεόμενοι: ὠχροὶ τὰ πρόσωπα, πλὴν τῶν μήλων. τάδε γὰρ ἐρευθῆ. ἱδρῶς περὶ μέτωπον καὶ κληῖδας: βὴξ συνεχὴς, βιαίη: ἀναγωγὴ σμικρὴ, λεπτὴ, ψυχρὴ, ἰκέλη ὁκοῖόν τι καὶ ἀφροῦ ἐπάνθισμα. τράχηλος οἰδέει πνεύματος πρήσι. ὑποχόνδρια ἀνεσπασμένα. σφυγμοὶ σμικροὶ, πυκινοὶ , πιεζεύμενοι: ἰσχνὰ σκέλεα: κἢν ὑπερταθῇ τάδε, ἀπέπνιξέ κοτε ἐπιληπτικῷ τρόπῳ. ἢν δὲ ἐς ἀγαθὸν τρέπηται, βὴξ μακροτέρη καὶ ἀραιοτέρη. ἀναγωγὴ πλεύνων τε πύων καὶ ὑγροτέρων: κοιλίης τάραχος πολλῶν ὑδατωδέων: οὖρων ἔκκρισις πολλὴ, κἢν ἐς ὑπόστασιν μηδέκω ἥκῃ: φωνὴ γεγωνοτέρη , ὕπνοι αὐταρκέες, ὑποχονδρίων ἄνεσις: ἦκέ ποτε πόνος ἐς μετάφρενον ἐπ᾽ ἀνέσι. ἆσθμα ἀραιὸν, λεῖον, κερχνῶδες. ὧδε μὲν οὖν διαδιδρήσκουσι τὸν ὄλεθρον ἐν δὲ τῇσι ἐπανέσεσι, κἢν περιΐωσι ὀρθοστάδην, τοῦ πάθεος φέρουσι ξύμβολα..." [16].

(…The symptoms of its approach are heaviness of the chest; sluggishness to one's accustomed work, and to every other exertion; difficulty of breathing in running or on a steep road; they are hoarse and troubled with cough; flatulence and extraordinary evacuations in the hypochondriac region; restlessness; heat at night small and imperceptible; nose sharp and ready for respiration. But if the evil gradually get worse, the cheeks are ruddy; eyes protuberant, as if from strangulation; *a râle* during the waking state, but the evil much worse in sleep; voice liquid and without resonance; a desire of much and of cold air; they eagerly go into the open air, since no house sufficed for their respiration; they breathe standing, as if desiring to draw in all the air which they possibly can inhale; and, in their want of air, they also open the mouth as if thus to enjoy the more of it; pale in the countenance, except the cheeks, which are ruddy; sweat about the forehead and clavicles; cough incessant and laborious; expectoration small, thin, cold, resembling the efflorescence of foam; neck swells with the inflation of the breath(*pneuma*); the precordia retracted; pulse small, dense, compressed; legs slender: and if these symptoms increase, they sometimes produce suffocation, after the form of epilepsy. But if it takes a favourable turn, cough more protracted and rarer; a more copious expectoration of more fluid matters; discharges from the bowels plentiful and watery; secretion of urine copious, although unattended with sediment; voice louder; sleep sufficient; relaxation of the precordia; sometimes a pain comes into the back during the remission; panting rare, soft, hoarse. Thus, they escape a fatal termination. But, during the remissions, although they may walk about erect, they bear the traces of the affection…)

At the Roman ages the Greek physician in the "De Materia Medica" (Περί ύλης ιατρικής) of Dioscorides Pedanio (Διοσκουρίδης Πεδάνιος, 40-90 b.C.), the Greek doctor who is considered the father of pharmacology, influenced by the eminet phycisian, Asclepiades of Bithynia (Ἀσκληπιάδης της Βιθυνίας, 124-40 b.C.) reports drug therapies for various pathologies similar to allergic ones; for example, he recommended mandrake for asthma therapy [17-20]. Also, throughout history, many great personalities suffered from allergies. Food allergies were well-described by the ancient Roman philosopher and poet Titus Lucretius Carus (99-55 b.C.). In his philosophical poem, *De rerum natura* (*On the nature of things*), a didactic work about the tenets and philosophy of Epicureanism, he observed an excessive reactivity to common substances and wrote "*what is food for some may be fierce poisons for others*" [19, 21].

Allergic diseases and respiratory symptoms were mentioned by Galen of Pergamus (Γαληνός **ὁ** Περγαμηνός, 129-216 a.C.). He agreed with the Hippocratic theories on these diseases and with the Aretaeus' observations. Furthermore, it was Pliny the Elder (23-79 a.C.) who gave a significant contribution in understanding that pollen was a source of respiratory distress. He recommended ephedra in red wine for asthma, blood of wild horses and fox liver in red wine, or millipedes soaked in honey [17, 20].

Familiarity for allergic diseases characterized the family of Emperor Tiberius Claudius Caesar Augustus Germanicus (10 b.C.-54 a.C.). He suffered himself from chronic rhinoconjunctivitis. Auguste, his great-grandfather and founder of the Empire, suffered from pruritus (itching related to a skin condition or general condition), seasonal rhinitis and breath-

ing problems. Claudius' son, Britannicus, was highly allergic to horses' skin. This a typical case of recurring presence of pathologies of allergic nature in a family, that today we could define an atopic family [22].

3. ALLERGIC SYNDROMES IN THE MIDDLE AGES

Subsequently in the Middle Ages there were many Byzantine medicine texts which described allergic pathologies and their treatment such as *"Ιατρικαί Συναγωγαί"* (Collectiones medicae) by Oribasius of Pergamum (Ορειβάσιος ὁ Περγαμηνός, 325-403 a.C.), "*Ιατρικά Βιβλία Ἑκκαίδεκα"* (Sixteen Books on Medicine) by Aetius Amidenus (Αέτιος ὁ Αμιδηνός, 502-575 a.C.), "*Θεραπευτικά 12 βιβλία"* (On Theurapetics, 12 books, later in Renaissance it is called Alexandri Yatros Practica) by Alexander's of Tralles (Αλέξανδρος Τραλλιανός,525-605 a.C.), "*Πραγματείας ιατρικής βιβλία επτά*" (Epitomae medicae libri septem*)* by Paul of Aegina (Παύλος ὁ Αιγινήτης, 625-690 aC), "Σύνοψις εν Επιτομή της ιατρικής απάσης τέχνης" (Synopsis in an Epitome of all Medical Art) 297 chapter by Chrysobalantes Theophanes or Nonnos (Χρυσοβαλάντης Θεοφάνης ἡ Νοννός, 10th century) and the "Μέγα Δυναμερόν" " (Great Dynameron or Medicamentorum Opus) by Nikolaus Mirepsus Actuarius (Νικόλαος Μυρεψός Ακτουάριος, 13th century) [17, 18, 23, 24].

During the Middle Ages, Arab and Persian physicians were interested in allergic syndrome, particularly they linked some form of allergy with a specific season. The Iranian Rhazes (late 9th century-early 10th century a.C.), described that his philosophy teacher suffered from sneezing, stuffy nose and intense pruritus. He underlined that these symptoms often worsen during spring: for this reason, he recommended people suffering from the same problems to avoid strong perfumes and certain plants (such as roses or basil) [22]. In his "*treatise on asthma*", written in 1190 a.C. the Jewish physician and philosopher Moses Maimonides, chief doctor of the Sultan Saladin, described allergic asthma as a seasonal disease, characterized by sudden bouts of breathlessness; he prescribed to the Sultan's son, who was an asthmatic patient, a treatment based on copious amounts of chicken soup, sweetened barley porridge and sexual abstinence [25, 26].

Allergic diseases have marked the history of some components of the English monarchy. When King Richard Lionheart died, his brother John Lackland (1166-1216 a.C.) became the new king of England in 1199. In 1200 he married with the young Isabelle of Angouleme, thirteen years old. His wife, who strongly hated him, elaborated a plan for his assassination: she made him eat a compote of peaches knowing that he could not beat them, and concealed the taste by adding cider and wine: he died in few minutes for a fatal anaphylactic shock in 1216. Shortly after, in the 15th century, King Richard III, who was suffering from serious attacks of urticarial after ingestion of strawberries, decided to use his food allergy to accuse his opponents of treason, particularly Lord William Hastings. He organized a banquet inviting his most strong adversaries and put himself at risk including strawberries in the meal. As planned, he developed a sever urticarious reaction, and, after resolution of the symptoms, accused his opponents of assassination attempt: Lord Hasting was decapitated for this reason [26, 27].

4. MODERN PERIOD

Around 1530, Jerome Cardan, was an important Italian physician of that time: he was invited by the Primate of Scotland because he was suffering from perennial asthma. After he evaluated his medical history, particularly a clear history of onset of symptoms in the morning after waking up, and the surrounding environment, he understood that the cause of his allergic manifestations could be in his bed; for this reason, he recommended him to get rid of the feather bedding, concluding he was either allergic to feathers or dust mites. He quickly recovered from his allergic disease. This historical episode shows that, in the 16th century, there was already the consciousness that allergic symptoms could be related to environmental factors and not only to the organic ones [28]

A few decades later, two royal physicians were very interested in allergic respiratory symptoms and their possible treatment: Ambroise Paré (1510-1590), royal surgeon, and Leonardo Botallo (1530 -1587), royal physician. The first observed breathing difficulties when cats were in the same room, while the second noticed the same symptoms during spring, after the spring blooming. Botallo, in 1564, wrote a book on this topic, "*De catarrho commentarius*" where he explained which symptoms he observed in some patients after the inhalation of the smell of flowers [29].

"…pleasant smells have healing properties for diseases of the heart, brain and liver. Stimulating one of the five senses stimulates the whole being, and the pleasant smells that drive away the discomfort soothe the mind itself. Yet, odours are favourable to many are unfavourable to other ones. I know healthy men who react to the smell of roses with sneezing, headaches and such itchy nose that they cannot help but scratch their noses for two days…"

Bernardino Ramazzini (1633-1714), an Italian physician, considered by many to be the founder of occupational medicine, tried to understand during his medical career what triggered certain occupational allergies. He focused his attention on occupational diseases, describing in his treatise "*De moribis artificium diatriba*" (*Diseases of workers*) that certain illnesses were more frequent in certain professional categories, such as farmers, bakers and manufacturers of rosebuds. This is the first comprehensive text on occupational diseases, which describes the consequences on workers' body of several irritating chemicals, dust, metals and abrasive agents. He accurately described asthmatic symptoms among bakers, correlating them with the accumulation of the flour dust that bakers breathed daily accumulated in the airways. He believed that this dust formed a kind of dough in their lungs, preventing them from breathing properly [30].

Many cases of food allergy were described by Robert William, a British physician, at the end of the 18th century. He observed some fatal cases of anaphylactic shock in his patients, suspecting the ingestion of crustaceans as the main cause. In 1819, John Bostock first described "hay fever" as disease of the upper respiratory tract, thinking it was caused by the effluvium from new hay during summer. In 1869, Charles Blakely, who was afflicted by "hay fever" himself, applied hay pollen through a skin's abrasion, performed the first allergological skin test [31].

5. THE DISCOVERY OF ANAPHYLAXIS

It is only in the twentieth century that two scientists understood that the exaggerated response observed when they tried to immunize animals with exogenous protein extracts against infectious diseases was probably due to an unknown mechanism that they named "*anaphylaxis*" [31-33]. particularly, the story of the discovery of the physiopathology of allergic mechanisms and of the chemistry and physiology of its most important mediator, histamine, started with Charles Richet and Paul Portier's description of allergic phenomena in 1902 [32-34].

Charles Richet (1850-1935) was a French physician. He studied medicine in Paris, he obtained two doctoral degrees in medicine and science in 1869 and in 1878, becoming Professor of physiology nine years later. In 1898 he started researching about the effect of eel serum's injection in dogs. The aim of the studies was to immunize the dogs against toxins. He observed that the first injection had no consequences, instead after the second and third injections, some dogs developed an acute syndrome, often lethal [35]. He became even more curious in this reaction, so he decided to investigate it deeper by using a toxin from the *Physalia physalis* (Linnaeus, 1758) an *Siphonophorae* (an order of the *hydrozoans*),on animals. He was invited by Prince Albert I of Monaco aboard his yacht 'Princess Alice II': the Prince, who was very interested in oceanic studies, allowed him to use the boat's laboratory. It was on that occasion that he met Paul Portier (1866-1962), another French physician who attempted the same medical school in Paris in 1889, becoming Professor of physiology at the Sorbonne in 1920. They started talking about oceanography and properties of the *Physalia* tentacles, deciding to carry out some experiments on ducks and rabbits using extracts of the jellyfish in order to study their great toxicity and to understand the exact mechanisms of their sudden deaths [36]. Charles Richet wrote about his researches:

"…the tentacles, cut close to the body, were placed in glycerine, dissolving and extracting the active principle. One fraction of these Physalia extracts contained a substance which was called 'hypnotoxin', which induced very painful urticarial reactions after contact with the skin, coupled with a drop in body temperature and somnolence…".

When Richet and Portier came back to their University's laboratories in Paris, they could not obtain a large amount of *Physalia*'s tentacles in the city, so they continued their researched by using tentacles of the "*Anemonia sulcata*" (a sea-anemone of Genere Actinia L. 1767) which were very similar to the jellyfish ones but easier to find. Richet described the toxic effects of these extracts in several dog experiments. He observed any effect after the first injection, but after he repeated the second injection of a small amount of the toxin extracts, some dogs suddenly died, in the same way of the first experiments with the *Physalia* extracts. So, he described two different toxins, the "*thalassin"*", able to induce violent pruritus and urticaria but that was not fatal, and the "*congestine*", which led to an intestinal congestion and cardiovascular alterations with a lethal outcome. To underline that these injections on animals had no protective effects, unlike vaccines, but only bad ones, he called this phenomenon "anaphylaxis", introducing it in the medical field, in antithesis to prophylaxis [37-39]. One of these experiments was described in a Richet's text as:

"One dog (Amphitryon) of 31 kg received 1.6 cc on 8 March 1902 of this liquid (corresponding to 0.8 cc of tentacles) and he died on the third day. If one admits that only 10% of the extract of the tentacles corresponds to solid material, 0.08 g are sufficient to poison the dog weighing 31 kg; therefore, the minimal quantity per kg dog to produce fatal effects are 0.0025 g out of the total of extractable substances of the tentacle".

Portier's most important experiment, described in his article in 1904, was performed on a strong and healthy dog (called Neptune) on January 14 and 17, 1902. The first injection was tolerated with 'almost no consequence'. After 22 days, on February 10, Neptune received the same dose of the same extract: it started gasping and wheezing, the animal was agonized, was not able to stand and lay on his side, developed bloody vomiting and died within 25 min, as described by Portier himself [32].

"…Je prendrai notamment pour exemple le chien Neptune, gros matin á poil ras, très vigoureux, qui, après avoir reçu, 22 jours auparavant la dose de 0,10 qui ne l'avait presque pas rendu malade, reçoit du même liquide la même dose de 0,10. Alors, aussitôt, quelques secondes après que l'injection a été terminée, il est extrêmement malade: la respiration devient angoissée, haletante. Il peut à peine se trainer; se couche sur le flanc, est pris de diarrhée et de vomissements sanguinolants. La sensibilité est aboulie, et il meurt en vingt-cinq minutes. Or, chez des chiens non injectés antérieurement, des doses dix fois plus fortes, 1 cc par kilogramme, ne tuent pas les animaux avec cette même rapidité…"

(…I will take as an example the dog Neptune, big, shorthaired, very vigorous, who, after receiving, 22 days before, the dose of 0.10, without any consequence, received another dose of 0.10 of the same extract. Immediately, few seconds after the injection, he became extremely sick: the breathing became short, panting, difficult. He can barely drag himself, lying on its side, with diarrhoea and hematemesis. Its sensitivity is abolished, and it dies in twenty-five minutes. Instead, in dogs not previously injected, a ten times higher dose, 1 cc per kilogram, do not kill animals with the same speed...)

When Portier informed Richet of his experiment, they instantly understood they discovered a new phenomenon: they tried to find a name for this exaggerated body's reaction to express "lack of protection" against toxins. Finally they selected the term "*anaphylaxis*" (*αναφυλαξία*) from the privative alpha in Ancient Greek "**ἀνά**", meaning "without" and "**φύλαξις**" which means "protection". This new medical terminology rapidly spread all over the world and it continues to be used in the modern allergologycal language [40].

Richet and Portier's description of anaphylaxis was the starting point to understand the mechanisms of immunological reactions and of the central role of histamine as the biochemical mediator. Their experiments clearly demonstrated that the first dose of a protein extract injected into a susceptible animal was able to strongly increase sensitivity to it after an opportune incubation period: as an example, after

injection of horse serum into the guinea pig, no reaction was observed if the time interval was less than 6 days and the reaction was maximal after 14 days. Richet affirmed in his texts that the two essential and sufficient conditions for anaphylaxis were: the increased sensitivity to a poison after previous injection of the same poison and an incubation period necessary for this state of increased sensitivity to develop [32, 33, 36].

Charles Richet received the Nobel Prize in 1913 for his researches on anaphylaxis phenomenon [39, 40], but he could not identify the exact pathogenic mechanism; in fact, he just concluded that this exaggerated reaction of the animals' organism was just a lack of protection to the poisonous effect different toxic substances. When he was awarded the Nobel Prize, he modestly affirmed:

"The discovery of anaphylaxis is not at all the result of thinking, but of simple observation, almost accidental. It had no other merit than that of not refusing to see the facts which presented themselves before me completely evident"

Despite Richet is considered the first scientist to discover the anaphylactic reactions, there were previous descriptions of these during the 19th century by many other authors of the heterologous serum injection's consequences. In fact, Emil von Behring remarked in 1914 that Richet's report described nothing else than what he had previously called "*hypersensitivity*". For this reason, we must cite the first descriptions about the human body's exaggerated reactivity to innocuous exogenous stimuli of François Magendie, (1783-1855), a French physiologist, who repeatedly injected dogs with egg albumin in 1839, observing their sudden death [41-43] after some decades, in 1869, a German student, Adolf Creite, used rabbits for his experiments, injecting a small amount of sheep, goat, cat, chicken and duck's serum: he observed different consequences on animals, such as malaise, haematuria, and, sometimes, their sudden death. In the same period, Leonard Landois, the German director of the Physiological Institute at the University of Greifswald, reported similar results after his laboratory's experiments on animals; in 1894, Abraham Flexner, who founded a private medical school in which he applied his alternative ideas about education, in contrast with the standard model of education that focused on mental discipline and a rigid structure, injected dog serum into rabbits, observing the same characteristics of what after Richet called "anaphylaxis". One of the most tragic event was probably the quick death in few minutes of the 2-years-old son of Robert Langerhans (1859-1904), a German pathologist, after the subcutaneous injection of 1.2 ml of Behring's "*Heilserum*" by his unbelieving and powerless father in 1896 [44, 45].

6. THE MODERN ERA OF ALLERGOLOGY

Anyway, this continuous going-on of researches about the effect of exogenous extracts on animals and observations on anaphylaxis phenomenon is provided a new focus in scientific research about allergic diseases and is considered the birth of modern Allergology.

The discovery of the phenomenon of anaphylaxis showed that by immunization harmful events and severe disease could also be induced. It was in 1906 that and Clemens von Pirquet, an Austrian paediatrician, coined the term "*Allergy*" (αλλεργία) after he observed several "strange" symptoms in diphtheria patients after the horse serum antitoxin's injection, from the Greek term "ἄλλος" (allos) which means "deviation from the original state"; in fact, he recognized allergy as an adverse reaction of the human's body to a harmless substance [45, 46].

7. THE DISCOVERY OF HISTAMINE AS A BIOCHEMICAL MEDIATOR

Sir Henry Hallett Dale (1875-1968) was the first scientist to understand that the symptoms of anaphylaxis were not caused by the effect of the toxin itself, but rather some biochemical mediator in the animal's organisms, humans included. He was a British physician who studied at the Trinity College in Cambridge. He had been working since 1903 in the laboratory with E.H. Starling at the University College in London and collaborated with Paul Ehrlich's laboratory in Germany. In 1904, he became the Director of the Wellcome Physiological Research Laboratories (WPRL). In 1910, Dale and a colleague, the chemist George Barger, were the first to announce during the International Congress of Physiology in Heidelberg the discovery of histamine. He showed what he observed during an experiment's bacterial contamination: an unknown contaminant of ergot generated by bacterial action was able to cause contraction of cat uterine strips. He was the first to isolate, with George Barger, the unknown chemical and to examine it physiologically: they identified a *β*-iminazolyl-ethylamine, synthetized by the amino acid histidine, and published their findings in both English and German [46-49]. The word "histamine" *(ισταμίνη)* comes from the Greek *"ιστός" (istos*) which means "tissue", due to its abundance in the body's tissues. He studied in his laboratory the histamine's effect upon the smooth muscle of different organs, a mild stimulating effect on the heart tissue and the absence of an effect on skeletal muscle. He started studying the physiological role of a histamine, proposing for the first time the theory that it was the principle mediator involved in anaphylactic shock. Dale and Barger's discovery of histamine and the development of a chemical technique to produce a high yield of the amine by using the bacterial putrefaction of pancreas encouraged others researches to investigate the chemical, physiological and pharmacological properties of this new molecule and so important biochemical mediator. Other chemical colleagues, Arthur Ewins from the WPRL and Frank Pyman, from the WCRL (Wellcome Chemical Research Laboratories), even more intrigued by the compound, joined the investigation and artificially synthesised histamine and a wide range of its analogues, all of which were then screened for therapeutic properties [49, 50].

In the Dale's following researches on histamine with his colleague, Patrick Laidlaw, he noticed how this compound seemed, ambiguously, to display both vasoconstrictor and vasodilator properties, depending both with the species of animal used and the type of vascular bed examined [51, 52]. For example, both mouse and rat tissues were not very responsive to histamine's action, instead both guinea-pig and human organs were extremely sensitive, particularly the non-pregnant uterus of the guinea-pig. Moreover, the rat uterus responded *in vivo* and *in vitro* by relaxing, whilst other

mammalian uteri contracted strongly [53, 54]. Not surprisingly, they concluded that its action "appears a somewhat complicated one!". However, their important observation of the histamine's effects on several different tissue made an important connection with the effects caused by histamine *in vivo*, including peripheral vasodilation, bronchiolar constriction, tachycardia and a drop in rectal temperature, the same observed during an anaphylactic reaction [54, 55].

At that time, histamine was not known to occur naturally in the animal body. They thought it was something introduced in the body from an exogenous source, particularly by a bacteria contaminant. Barger and Dale did try to find the endogenous source of histamine's production by examining the intestinal mucosa. Other correct results on the physiological or pathological mechanisms of allergic reactions were delayed by the erroneous finding of a bacillus able of producing β-I [histamine] from histidine in the duodenum [56-59]. They probably found histamine in this tissue due to bacterial decomposition going on in the intestine, so, unfortunately, they could not understand the endogenous production of histamine by lymphocytes in many tissues of the body. Dale and Barger did not attempt to find a further source of histamine, as Dale commented many years later:

"Why did we not clinch the matter then by trying other tissues? A few experiments would have shown us the richness of the lung for example, in a similarly active substance; and we could certainly have found histamine as easily in such a clean tissue as in one under suspicion [i.e. the intestine]. I cannot say why; but I suppose that we did not then see the importance and interest of the matter. We seem also to have had plenty of other things to do."

With the last sentence Dale intended to specify he had many administrative responsibilities as Director of the WPRL but also the fact that he was involved in laboratory researches on other projects: when histamine's paper appeared in a volume of the *Journal of Physiology*, he was simultaneously the co-author of another paper on cardiovascular effects of vagal stimulation and another paper on the actions of sympathomimetic amines. Work on histamine was a lower priority for its laboratory, instead he devoted a considerable amount of effort to acetylcholine, work that lead directly to his Nobel Prize [52, 53, 55].

Soon after, Henry Dale also observed that in the allergic reactions must be involved some types of serum factors, on which was based the individual hypersensitivity, but he cannot identify them; in fact, in 1913, he demonstrated that anaphylactic contraction of smooth muscle could be caused by prior cellular sensitisation to an antigen. He was studying the physiological effects of histamine, using as an *in vitro* bioassay the isolated virgin guinea-pig uterus, which he observed to be highly sensitive to histamine [53]. One of his control substances was fresh horse serum: he observed that some of the uteri had very strong reactions to the horse serum in a very low dilution. So, he interrogated himself is there was any possibility that some of his experimental guinea-pigs had been previously treated with serum. In fact, he discovered that this was exactly what had happened. Animals used as controls for anti-toxin testing, that is, those injected just with horse serum, or low doses of anti-toxic serum for toxicity tests, were routinely destined for further use. This accidental use of a pre-sensitised animals to horse serum was one of the fortunate events in Dale's career. Moreover, Dale's theories on allergic diseases contrasted the humoral theories then in vogue. These theories postulated that the antigen–antibody reaction in the blood lead to the liberation of toxic products, so-called "*anaphylatoxins*" (*αναφυλατοξινες*), which were able to induce anaphylaxis typical signs [54]. He used a guinea-pig's uterus that had been highly sensitised to horse serum, removed all the tissutal blood with a perfusion using a Ringer solution, and finally he tested the responses of the smooth muscle to horse serum. He obtained the same contraction as the perfused tissue: this experiment was of critical importance in demonstrating that the antigen was not circulating in the serum, but was fixed in the cells and tissues. Despite Dale's demonstration of his theory, tensions continued throughout the next decade between supporters of the same theory and those of the circulating antigen–antibody theory [53, 54].

The presence in the serum of allergic people of something on which allergies are based was also demonstrated by a French physiologist, Nicolas-Maurice Arthus (1862-1945), who observed how repeated injections of sterile horse serum into the skin was able to cause an inflammatory reaction, characterized by redness, oedema, bleeding and necrosis in some cases. This form of "local anaphylaxis" is what today we call the "*Arthus phenomenon*". This intuition was confirmed by Prausnitz and Küstner in 1921 when they were able to transfer this hypersensitivity to fish via serum from one allergic individual to another non-allergic individual [60-62].

The identification of histamine marked a milestone in both pharmacological and immunological research, starting a new scientific period devoted towards finding ligands which could contrast the histaminergic activity. In 1937, Bovet and Staub identified compounds that antagonized the histamine's effect in allergic reactions. The Nobel Prize in Physiology and Medicine was awarded to Daniel Bovet in 1957 for the discovery of antihistamines (anti-H_1R) and to Sir James Black in 1988 for the identification of anti-H_2R antagonists. In 1953, James F.Riley and Geoffrey B.West identified the mast cell granules as the major storage of histamine and in 1967, Kimishige and Teruko Ishizaka explained the allergic process by discovering the role of IgE antibodies, the principal mediator in allergic reactions [62, 63].

In the following years, anaphylaxis was regarded as an experimental phenomenon after the "artificial" injection of proteins; some researches demonstrated that anaphylaxis-like symptoms could be elicited in animals not previously immunized by the direct injection of histamine in their circulation, but also through the injections of several substances, such as codeine and dextran, which caused a strong histamine release by the body's tissues. These symptoms were named "*pseudo-allergic reactions*" by Paul Kallós. In the same years, Coca and Cooke coined the term "*Atopy*" (*ατοπία*), from the Greek term "*ἄτοπος"* (*atopos*) which means "out of place", to distinguish 'natural' occurring hypersensitivity from the "artificial" symptoms of anaphylaxis in animal experiments [60, 61, 63].

This distinction between allergic reactions and pseudo-allergic ones was initially confused: it was only at the begin-

ning of the 21th century that both the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (WAO) tried to define anaphylaxis' phenomena in a very clear way, based on clinical symptoms and mechanism evolved in elicitation, making a distinguish between an allergic and a non-immune anaphylaxis, formerly called a "pseudo-allergic reaction". This distinction helped to make the differential diagnosis for other similar pathological conditions. Non-immunological mechanisms involve substances or factors which in rare cases directly cause mast cell and basophil degranulation such as the contrast media used in radiology, opioids, vancomycin. Other pathologies that manifest in a similar way to anaphylaxis can be the Histamine fish syndrome and anisakiasis [64-71].

8. MODERN RESEARCHES ON MAST CELLS ROLE AND RECEPTORS

Recent evidences add new dimensions to the roles of mast cells as regulators of tissue homeostasis, underlining both positive and negative aspects. Mast cells are tissutal innate immunity's cells which play protective roles in host defence against parasites and bacteria, fungi, viruses, and arthropods [72-77]. Their products, such as proteases, protect against animal venoms or poisonous substances, including honey bees, scorpions, and reptile venoms [78]. Moreover, venom-specific IgE antibodies and IgE-mediated mast cell responses after re-exposure contribute to protection against lethal doses of venoms [79, 80]. They express a large variety of receptors to recognize and react to a wide spectrum of infectious pathogens and endogenous molecules in damaged or inflamed tissues.

More exposed tissues to the environment (skin, airways, gastrointestinal tract) are rich of these immunity cells, where they are stationed as local sentinels [72]. Mast cells granules contain histamine, heparin and a large amount of proteases, mainly serine proteases. All these substances are secreted into the interstitial space on mast cell activation. Proteolytic cleavage on different substrates result in either activation or inhibition, with a complex results that depends on the specific environment [81-83]. In response to proper stimuli, they can also release cytokines, chemokines, lipid mediators and growth factors (NGF, GM-CSF, PDGF, TGF-β, and VEGF). Mast cells are implicated in tissue remodelling and angiogenesis through release of these growth factors and specific proteases [84-86].

However, mast cells are potentially lethal cells on widespread activation, as occurs in fatal anaphylaxis. They are the main actors in the allergen-induced release and generation of allergic reactions mediators, which can quantitatively and qualitatively cause severe tissutal injuries in case of acute or chronic but sustained activation, as in chronic infections, tumoral growth's promotion [87, 88], autoimmune diseases, such as multiple sclerosis [89, 90]; and atherosclerosis [85].

FcεRI, the high-affinity receptor of IgE, is the primary receptor in mast cells that mediates allergic reactions. Aggregation of FcεRI through multivalent binding of allergen to IgE bound to the high-affinity IgE receptor promotes allergic inflammation by inducing rapid release of granules-associated mediators. This "*immediate hypersensitivity reaction*" is characterized by the rapid synthesis of lipid-derived inflammatory mediators (prostaglandin D2, leukotriene C4, PDGF) and the transcription of cytokines and chemokines that can promote inflammation and regulate tissue remodelling. Mast cells degranulation in the skin results in a wheal-and-flare reaction, in the airway causes smooth muscle contraction, mucus secretion and increased vascular permeability. If systemic, allergic mediators release can bring to severe vasodilatation and hypotension and extensive vascular leakage among other effects. These early responses can transition into a late-phase reaction hours later that is associated with an influx of circulating cell types, which can promote further inflammation [73, 74, 91].

Non-classical mechanisms of anaphylaxis presents on mast cells involved immunoglobulin receptors other than FcεRI, anaphylatoxin receptors and complement activation, which act in synergy with antibody-induced reaction [92]. Several non-IgE receptors are implicated in mast cells activation during immediate local or systemic reactions, such as the Toll-like receptor (TLRs), the NOD-like receptor, which provide the capacity for recognition of a large variety of microbes and parasites [76, 93] the Mas-related G protein–coupled receptor X2 (MRGPRX2), the adhesion G protein–coupled receptor E2 (ADGRE2) and the IL-33 receptor. Recent studies stressed the importance of them in the physiopathology of allergic diseases, particularly in the modulation of mast cell responses.

Many compounds can activate mast cells degranulation and stimulate their production of prostaglandin D2 and chemokines and cytokines, including IL-2, IL-3, IL-4, IL-6, IL-31, TNF-a, and GM-CSF [94-96]. They were originally named as ''histamine liberators or secretagogues'', such as polybasic compounds, pharmacologic agents, antimicrobial peptides and insect venom's components, but also endogenous peptides released by other environmental cells, such as the eosinophil peroxidase and major basic protein, and many neuropeptides such as substance P, vasoactive intestinal peptide, neuropeptide Y, somatostatin. In addition, some studies concerning the activation of mast cells through neuropeptides and antimicrobial host defense peptides conducted on rats rat peritoneal mast cells, LAD2 cells, human mast cell line or derived human mast cells (*in vitro* CD34), showed that neuropeptides and antimicrobial host defense peptides lead to the mast cell chemotaxis and degranulation and subsequently to cytokine generation through pathways that activated the pertussis toxin (PTx) -sensitive G proteins. In particular MRGPRX2 couples to both pertussis toxin-sensitive and insensitive signalling pathways, most likely involving $G_{\alpha i}$ and $G_q\alpha$ to induce degranulation, and also results in $G_{\alpha i}$ dependent production of the pruritogenic cytokine IL-31 through the MAPK- and Akt-dependent pathways. [97].

Recent studies they had tried to prove, that these cationic mast cell activators act on human mast cells in a $G_{\alpha i}$ subunit–dependent manner, by activating PLCβ, phosphatidylinositol-4,5-bisphosphate 3-kinase, rapid and transient intracellular calcium mobilization and immediate granules content's secretion, through MRGPRX2. However, linkage between MRGPRX2 and degranulation via subset of G proteins in mast cells remains uncertain [73, 96-98]. This newly discovered receptor stimulation in mast cells might contribute to

their roles in innate and adaptive immunity, neurogenic inflammation, pain and itch, but also in tissues with chronic allergic diseases, such as chronic idiopathic urticaria, asthma and periodontitis, where an increased number of mast cell expressing MRGPRX2 has been described [99- 101].

Another emergent mast cells receptor, the adhesion G protein–coupled receptor E2 (ADGRE2), also known as EGF-like module–containing mucin-like hormone receptor–like 2 (EMR2) or CD132, is considered a cellular sensor of mechanical stimulation, activated by mechanical vibration. Although its physiologic relevance is not completely understood, probably it might alert both resident and immune cells of a tissutal potential injury, for instance during parasite migrating through dermal tissues. First evidence of its important role in mechano-sensation was shown by demonstrating that a missense substitution from cysteine to tyrosine (pC492Y) is associated with the autosomal dominant vibratory urticaria (VU), a type of physical urticaria characterized by localized hives and systemic manifestations in response to a local stimulus of frictional nature [102, 103]. The patient-derived mast cells expressing the mutated receptor degranulate extensively on mechanical vibration.

IL-33 receptor (also known as ST2 long-form - ST2L) is mast cells receptor which recognizes Interleukine-33 produced by epithelial and other stromal cells of an inflamed tissue, but also by immune cells of the innate immune system as a potent inflammatory enhancer, including mast cells themselves and basophils. When IL-33 binds its receptor, it induces differentiation, survival, chemotaxis and cytokine production of these cells, amplification allergic inflammation [104-108]. In case of intestinal helminth infections, mast cells amplified response mediated by IL-33 production enforces Th2-lymphoid cells activation and facilitates worm's death and expulsion [109]. At the same time, this mechanism can be relevant and negative in allergic responses to food or airway allergens, in patients with topic dermatitis, cutaneous sensitization to food allergens and food-induced anaphylaxis [110].

Evidence also suggests that IL-33 receptor also mediate anti-inflammatory functions under certain circumstances, depending on the pathophysiologic situation, with an immunomodulatory function which limits excessive inflammation to re-establish tissue integrity; for instance, in the absence of IgE cross-linking it can limit inflammation [111-114].

9. HISTAMINE'S RECEPTORS

During the second half of the 90s and the beginning of the 21th century, by using selective agonists and antagonists, four distinct separate rhodopsin-like G protein-coupled receptors were identified, each one with a different physiological role: first the H1 and H2 receptors (H_1R and H_2R), and, more recently, the H3 and H4 receptors (H_3R and H_4R). Each of the histamine receptors produce a functional response, but their mechanism differs. The H1 receptor couples to Gq/11 stimulates the formation of inositol 1,4,5 trisphosphate and 1,2-diacylglycerol by phospholipase C, whereas the H2 receptor interacts with Gs to activate adenylyl cyclase. The H3 and H4 receptors couple to Gi proteins to inhibit adenylyl cyclase, and to stimulate MAPK in the case of the H3 receptor [115, 116]:

a). The human H1-receptor gene resides on chromosome 3. It is widely distributed in the periphery, in the airway, intestinal and vascular smooth muscle where it stimulates contraction (bronchoconstriction and vasoconstriction) [115-117]. It is also found in the adrenal medulla, vascular endothelium and heart and throughout the central nervous system, including the cerebral cortex, spinal cord and cerebellum. It is involved in the control of several brain functions (sleep/wakefulness, thermoregulation, hormonal secretion, food intake and memory) [117]. The preferential expression of H_1R by several immune cells (mast cells, basophils and eosinophils) and its involvement in the development of allergic symptoms and inflammation after its exaggerated activation and an abnormal release of histamine in the involved tissues provide the rationale for the use of anti-H_1R antagonists in allergic and in other immune-related disorders. Until the 70s, several potent antihistamines has been developed to antagonize this receptor (Anti-H_1R). By 1937, the first antihistamine (H1-receptor antagonist) had been synthesised by Etienne Fourneau: the thymo-ethyl-diethylamine. However, its activity was too weak, and it was too toxic for clinical use in the treatment. In 1942, Bernard N. Halpern synthesised the first clinically used antihistamine: the phenbenzamine. The first generation antihistamines, however, were useful in inhibiting allergic symptoms but with a strong side effect: they easily penetrated the brain, causing drowsiness as they opposed the reaction of histamine with the H_1 receptors in the CNS which cause wakefulness. Elimination of the blood-brain-barrier passage has resulted in many new, non-sedating, H1-antagonists.

b). Ash and Shild in 1966 proposed the existence of two subtypes of histamine receptors because they observed that the classical antihistamines did not antagonise every histamine-induced effects. Few years later, Black *et al* succeeded in the synthesis of new compounds which were able to block the histamine-induced effects of the heart and on the stomach, where it is express the H2-Receptor subtype. These compounds (cimetidine, ranitidine, famotidine) are used in the therapy of gastric ulcers. Its gene resides on chromosome 5. It is expressed in a variety of tissues: on parietal cells, located in the stomach lining, which are the main responsible for regulating levels of gastric acid (histamine stimulates the release gastric acid, excess of which can result in stomach flu), but also on heart, uterus and vascular smooth muscle cells (histamine encourages smooth muscle relaxation). It is found on neutrophils and in the lungs.

c). The H_3 -Histamine Receptor was discovered in 1983 by Arrang and co-workers. This receptor regulates the release and synthesis of histamine itself, but, at the same time, it has a regulatory role in the release of other neurotransmitters. It is expressed in different areas of the CNS (basal ganglia, hippocampus, cortical areas), in the peripheral nervous system, in the gastrointestinal tract and in the cardiovascular system. With the recent progress that has been made in its characterisation, many

pharmaceutical companies have continually active H3 receptor ligands development programs for many applications, including dementia, migraine, and obesity.

d). H_4 - Histamine Receptor was discovered in 2001. It has high sequence identity with the H3-receptor and they are also similar in gene structure. It is mainly expressed in bone marrow and peripheral leukocytes (mast cells, dendritic cells, eosinophils) and in the spleen. It is involved in immune and inflammatory responses, chemotaxis and white blood cell release from bone marrow [118-120].

10. ACTUAL ALLERGIES TREATMENT GUIDELINES AND FUTURE PERSPECTIVES

Today, allergies are even more frequent in all age groups of population due to the ever-increasing use of chemical substances in food, pollution, and cross-reactivity with natural substances. Allergies and asthma are often considered "the epidemic of the 21st century". The best way to keep allergic symptoms under control is often to avoid exposure to allergens (food, animals, pollen, dust mite), although this is not always practical and possible. Today, medicine can keep track of allergies with symptomatic remedies, but a definitive treatment is not possible yet. Antihistamines are the main drugs for allergies, both during an allergic reaction and to prevent it [121, 122]; decongestant can be used as a short-term treatment for a blocked nose caused by an allergic reaction. Lotions and creams can be applied to reduce itchiness on the skin in case of eczema, contact dermatitis and urticaria; steroids (topic and systemic use) can help reduce inflammation caused by an allergic reaction. Finally, immunotherapy (desensitisation) may be an option for people with severe and persistent allergies with uncontrollable symptoms using the measures above. It involves being given occasional small doses of the allergen, either as an injection or as drops or tablets under the tongue, over the course of several years to help the body get used to the allergen so it does not react to it so severely [123].

Severe allergies may bring to anaphylactic shock. Epinephrine (adrenalin) as a treatment of choice has been known for more than a hundred years. Guidelines for acute treatment of anaphylaxis have been developed at the national and international level. We hope that the progress made in understanding the mechanism of action of the histamine response will lead to better targeted treatment options in future.

CONCLUSION

From the first researches historical anecdotes on allergy and the first approximate hypothesis of the fundamental involvement of mast cells in allergic phenomena and anaphylaxis, many steps forward have been made till new findings related to non-IgE related-receptors, such as MRGPRX2 and ADGRE2.

In the last few years, modern research emphasizes a new vision of these ancient cells' protective role for the host immunity, considering mast cells final activity as a perfect integrated response to a compilation of receptors' signals coming from the environment. Depending on the physiological or pathological interactions with other signals, this response can either bring a positive effect or a lethal or simply unwanted outcome. A new approach has been the development of humanized mouse models which gave the opportunity to study human mast cell biology and responses in a humanized physiologic context, in order to better investigate possible human-specific therapies in preclinical studies in allergic reactions and other disorders in which mast cells play an important role [124-127].

To understand even more better, the MRGPRX2's biologic/pathologic relevance and involvement in allergic diseases, further researches are needed on human mast cells, as also the inhibitory receptors role in inhibiting allergic mechanisms. Considering their fundamental role in biological systems, in host's deference against parasites and venoms, pharmacologic approaches directed at decreasing tissue mast cell numbers or perhaps ablating the mast cell compartment should be carefully avoided [127], instead, many efforts should be made trying to understand how to modulate cellular activity for host's benefits in those diseases in which mast cells are major actors.

AUTHORS' CONTRIBUTIONS

Conceptualization, I.A.C. and L.S.; validation, L.B. and L.S.; investigation, I.A.C., F.C., L.S. and L.B.; resources, I.A.C.; data curation, I.A.C., F.C., and L.B.; writing—original draft preparation, I.A.C. and F.C.; writing—review and editing, L.B. and L.S.; supervision, L.S.; project administration, L.S. and L.B.

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