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Phosphodiesterase-4 in Atopic dermatitis, systematic review

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Abstract

Introduction: Atopic Dermatitis (AD) is a chronically relapsing, non-contagious, pruritic skin disorder that causes dry and flaky skin with thickening. Phosphodiesterase-4 is one of the main targets for treatment of AD.

Objective: To represent a solid comprehensive overview about Phosphodiesterase-4 levels in Atopic dermatitis.

Source: Web of Science database core collection, and Scopus database.

Methodology: Systematic review papers with or without a meta-analysis on the Phosphodiesterase-4 levels in Atopic dermatitis have been included. The estimated plausible hazard of unfairness was performed by recording, reportage and methodological quality of the selected systematic reviews.

Design: A systematic review **Data sources**: An electronic search of Scopus, and the Web of Science was completed up to June 2021. The data included basic characteristics, and related complications were examined and recorded.

Review methods: Eligibility and methodological quality of the studies were assessed by the authors independently.

Results: 64 review articles were recorded for both Phosphodiesterase-4 and Atopic dermatitis simultaneously in Scopus database while 66 review articles were recorded in web of science in June 2021.

Conclusion: The relation between Phosphodiesterase-4 and atopic dermatitis was confirmed whereas, Phosphodiesterase 4 (PDE4) regulates cyclic adenosine monophosphate in cells and has been shown to be involved in the pathophysiology of AD, making it an attractive therapeutic target.

Keywords: Phosphodiesterase-4; Atopic dermatitis; Systematic review; Meta-analysis

1-Introduction:

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritic erythematous skin lesions and associated cutaneous dysfunction (e.g., barrier-disrupted skin) ***(Berke et al., 2012)***. Patients suffer from eczematous skin lesions, persistent itching and sleep disorders. Starting usually at early childhood. The course of

AD is heterogeneous. In most cases, AD disappears before adolescence, but about 30% of patients show a chronic persisting course ***(Lauffer et al., 2016)***. Atopic dermatitis has a prevalence that ranges from 7% to 30% in children and from 2% to 10% in adults. AD and food, allergies have the highest incidence in the first two years of life. Sensitization to inhalant allergens is rare. In later childhood, the prevalence of AD and food allergies decreases while the prevalence of asthma, allergic rhinitis, and sensitization to inhalant allergens rises ***(Kijima et al., 2013)***.The prevalence of AD is increasing as do other atopic disorders. AD has been classified into 3 phases: infantile, childhood, and adult, each with characteristic physical findings. AD has a tremendously negative effect on the quality of life of patients as well as the family due to sleep disturbance. The condition also creates a great financial burden for both the family and society ***(Spergel, 2010).*** Peripheral leukocytes in patients with atopic dermatitis (AD) are associated with elevated phosphodiesterase-4 (PDE-4) activity, leading to production of proinflammatory mediators. OPA-15406 is a PDE-4 inhibitor with high selectivity for PDE-4 ***(Jon et al., 2016).***

PDE-4 has been associated with higher production of the proinflammatory mediators e.g., tumor necrosis factor-alfa (TNF-α), interleukin (IL)-17, -22, and interferon-gamma (IFN-γ) and lower production of the anti-inflammatory mediator IL-10 ***(Baumer et al., 2007).*** AD cannot be cured, but prompt and effective management, according to the guidelines of the American Academy of Dermatology, can greatly improve both the symptoms and the quality of life of affected individuals. ***(Hanifin et al., 2004).*** Recent use of antihistamines, emollients, and immunosuppressants as treatment options for AD in humans has reduced the use of corticosteroids ***(Ring et al., 2008).***

2. Objective

The objective of this review was to summarize and appraise the results of published research, to explore the effects of Phosphodiesterase-4 in Atopic dermatitis, in order to provide guidance for physicians in their daily management of patients.

3. Methods

3.1. Literature search

An electronic search of Scopus, and the Web of Science was completed up to June 2021. The data included basic characteristics, and related complications were examined and recorded.

3.2 Study Design:

Considering the limited studies, we reviewed cohort studies and randomized controlled trials. Studies were excluded if they met the following criteria: (1) Duplicate publications, (2) Case reports, (3)Contained insufficient information to extrapolate the data and (4)Full text was not available.

3.3. Selection of reviews:

The principle author screened retrieved titles and abstracts to identify potentially relevant reviews. The full texts of these studies were assessed independently by researchers for eligibility. Differences observed in the selection were resolved through a group discussion.

3.4. Selection Criteria:

The selection of studies was carried out in two phases. In the first stage, titles and abstracts were autonomously screened for selection by two reviewers based on predetermined inclusion and exclusion conditions and disagreements were resolved by dissuasion and consensus.

If the title met the eligibility criteria, the article was selected. If the title did not meet the eligibility criteria, the abstract was read carefully for compatibility. Only the latest version of an updated study was chosen. The references of the studies that met the eligibility criteria were manually screened for further published articles meeting the criteria. There were no attempts to hide the names of the authors or the journals.

Box 1. Inclusion and exclusion conditions:

The inclusion conditions were recorded as the

followings:

The exclusion criteria were as follows:

- Studies related to animals
- Publications represented as abstract only, editorials and correspondence sectors
- Duplicate publications,
- Case reports
- Contained insufficient information to extrapolate the data
- If f ull text was not available

3.5. Data Extraction and Evidence grading:

Data concerning the study quality, focused question, search results and outcomes were processed for extraction from articles fulfilling the selection criteria. The data was extracted, categorized, summarized and graded independently. Questions and dissimilarities between the authors were finalized through objective discussion followed by consensus.

4. Results and discussion

Atopic Dermatitis (AD) is a chronically relapsing, non-contagious, pruritic skin disorder that causes dry and flaky skin with thickening and increase in skin markings (lichenification) and intense itching (Figure 1). It usually affects flexural areas in children and adults (Figure 2) ***(Morikawa et al., 2016)***.

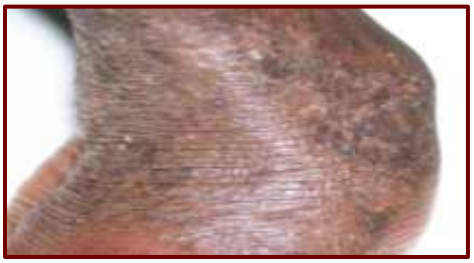

Figure (1): Lichenification (skin thickening and enhancement of skin markings) and scaling on the front of the ankle in an adult with chronic atopic dermatitis ***(Wollenberg et al., 2018)***.

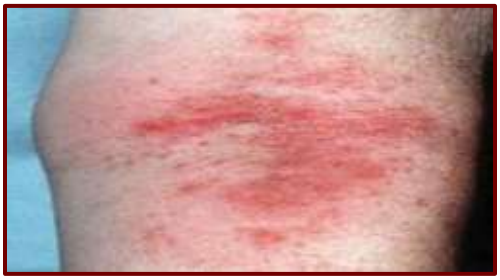

Figure (2): Atopic dermatitis. Flexural areas are common locations for recurrent atopic dermatitis in children and adults ***(Wollenberg et al., 2018)***.

Atopic dermatitis usually starts in early infancy, but an adult-onset variant is also recognized. Atopic dermatitis can have a significant impact on morbidity and the quality of life. For example, children may be affected by the itching and associated sleep disturbance, the social stigma of a visible skin condition, and the need for frequent application of topical medications and physician visits. As previously mentioned, it has been estimated that children with AD lose an average of 1.9 hours of sleep per night, and their parents lose an average of 2.1 hours of sleep per night. Other significant Problems reported in children with Atopic dermatitis include irritability, daytime tiredness, fearfulness, mood changes and dependence on parents for treatment and support ***(Morikawa et al., 2016)***.

Clinical features and Symptoms of AD:

The diagnosis of AD is based on the constellation of clinical features. It requires the presence of at least three major features and at least three minor features. (Table 1) summarizes the diagnostic features of AD ***(Morikawa et al., 2016)***.

Table (1): The diagnostic features of atopic dermatitis ***(Morikawa et al., 2016)***.

Major features

• Pruritus and excoriations (Characteristic rash in locations typical of the disease).
• Typical appearance and distribution of skin lesions.
• Intense itching.
• Facial and extensor involvement in infancy and early childhood.
• Flexural involvement and lichenification by adolescence.
• Chronic or frequently relapsing course (duration > 6 weeks).
• Personal or family history of atopic disorders, allergic rhinoconjunctivitis, food allergy, asthma or hay fever.
Minor features
• Increased susceptibility to skin infections, particularly S. aureus.
• Xerosis (dryness of the skin).
• Early age of onset.
• Multiple positive immediate prick skin test results.
• Ichthyosis, keratosis pilaris, hyperlinearity of palms.
• Nonspecific hand/foot dermatitis.
• Scalp dermatitis (e.g., cradle cap).
• Elevated serum IgE levels.
• Inflammation around the lips.
• Cataracts (anterior subcapsular) Keratoconus.
• Impaired cell-mediated immunity.
• Nipple eczema.

Atopic dermatitis usually begins during infancy. In approximately 50% of patients this illness develops by the first year of life, and in an additional 30%, between the ages of 1 and 5 years. In nearly 80% of patients with AD allergic rhinitis or asthma eventually develops later in childhood. Symptoms and signs vary from person to person. The most common symptoms are dry, itchy skin and red sensitive rashes inside the elbows, behind the knees and, on the hands and feet and on the face. Itching is the most imperative symptom of atopic dermatitis ***(Fiocchi et al., 2015)***.

The skin may be red, scaly, thick and leathery and contains small raised bumps, or leaks fluid and becomes crusty and infected. Atopic dermatitis may also affect the skin around the eyes, eyelids, eyebrows and lashes. Scratching and rubbing the eye area can cause the skin to redden and swell. Some people with atopic dermatitis develop an extra fold of skin under their eyes. Patchy loss of eyebrows and eyelashes may also result from scratching or rubbing as shown in (Table 2) ***(Morikawa et al., 2016)***.

Table (2): Skin features associated with atopic dermatitis ***(Morikawa et al., 2016)***.

Keratosis pilaris	small, rough bumps, generally on the face, upper arms, and thighs.
Atopic pleat (Dennie Morgan fold)	an extra fold of skin that develops under the eye.
Cheilitis	inflammation of the skin on and around the lips.
Hyperlinear palms	increased number of skin creases on the palms.
Hyperpigmented eyelids	eyelids that have become darker in color from inflammation or hay fever.

Lichenification	thick, leathery skin resulting from constant scratching and rubbing.
Ichthyosis	dry, rectangular scales on the skin.
Papules	small raised bumps that may open when scratched and become crusty and infected.
Urticaria	hives (red, raised bumps) that may occur after exposure to an allergen, at the beginning of flares, or after exercise or a hot bath.

Pathogenesis and Etiology of AD:

AD is a multifactorial disease. The interactions between susceptibility genes, the environment, defective skin barrier function, and immunologic responses influence the pathogenesis of AD. The pathophysiology is still poorly understood but three main hypotheses have been proposed regarding the development of the inflammatory lesions ***(Finberg, 2013; Dharmage et al., 2014; Wollenberg et al., 2016):***

1) The first suggests an immune dysfunction resulting in IgE sensitization.
2) Secondary epithelial-barrier disturbance or dysfunction which proposes a defect in epithelial cells leading to the defective barrier problem.
3) The current theory is an unidentified genetic abnormality. The role of genetics has been demonstrated in studies of families and twins ***(Finberg, 2013)***.

▪ **Immune dysfunction:**

Cytokines such as TNF-α and IL-1 from resident cells (keratinocytes, mast cells, and dendritic cells) bind to receptors on vascular endothelium, activating cellular signaling including the nuclear factor Kappa-light-chain-enhancer of activated B protein (NF-κB) pathway and inducing the expression of vascular endothelial cell adhesion molecules. These events initiate a process of tethering, activation, and adhesion of inflammatory cells to the endothelium followed by extravasation of inflammatory cells. Once the inflammatory cells have infiltrated into the tissue, they respond to chemotactic gradients established by chemoattractant cytokines and chemokines, which emanate from sites of injury or infection ***(Stuart et al., 2015)***. These molecules play a central role in defining the nature of the inflammatory infiltrate in AD ***(Buhl et al., 2015)***.Clinically unaffected skin in AD is not normal. It frequently manifests increased dryness and a greater irritant skin response than healthy controls. Unaffected AD skin contains a sparse perivascular T cell infiltrate not seen in normal healthy skin as shown in (Figure 3). Analyses of biopsies from clinically unaffected skin of AD patients, as compared with normal non atopic skin, demonstrated an increased number of TH2 cells expressing chemokine's like IL-4 and IL-13, but not IFN- γ ***(Zaiss et al., 2015)***.

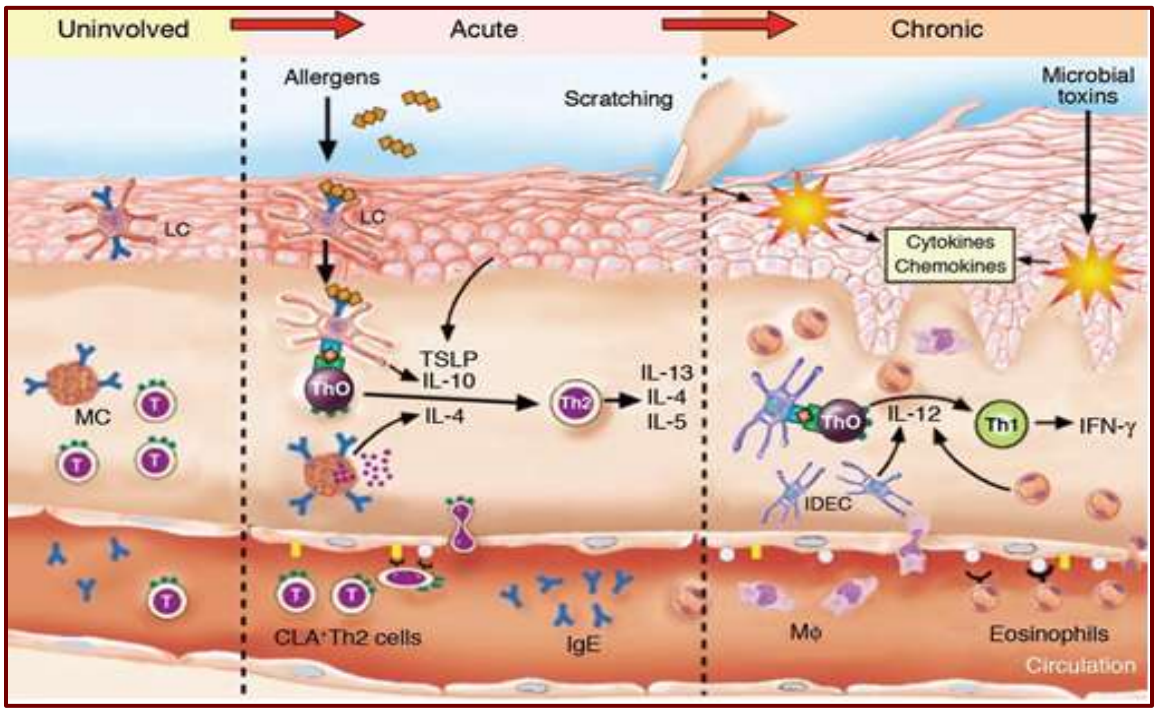

Figure (3): Immunologic pathways in AD ***(Noda et al., 2015)***.

▪ **Epithelial-barrier disturbances:**

The second hypothesis involves defective barrier function in the stratum corneum of AD patients. Researchers have noted differences in the skin of people with AD that may contribute to the symptoms of the disease. The outer layer of skin, called the epidermis, is divided into two parts: an inner part containing moist and living cells, and an outer part, known as the horny layer or stratum corneum, containing dry, flattened and dead cells ***(Nomura and Kabashima, 2016)***. Under normal conditions, the stratum corneum acts as a barrier keeping the rest of the skin from drying out and protecting other layers of skin from damage caused by irritants and infections. When this barrier is damaged, irritants act more intensely on the skin leading to the entry of antigens that result in the production of inflammatory cytokines and trans epidermal water loss is increased. The skin of a person with atopic dermatitis loses moisture from the epidermal layer, allowing the skin to become very dry and reducing its protective abilities ***(Nomura and Kabashima, 2016)***.

Thus, when combined with the abnormal skin immune system, the person's skin is more likely to become infected by bacteria (for example, *Staphylococcus* and *Streptococcus*) or viruses, such as those that cause warts and cold ***(Fiocchi et al., 2015)***.

▪ **Unidentified genetic abnormality:**

Defective lamellar bodies may be caused by abnormalities of ceramide production. It is not known whether the inflammation causes primary or secondary epidermal barrier breakdown, but with the knowledge that filaggrin is involved in epithelial disruption. It is thought that this finding leads to increased trans epidermal penetration of environmental allergens, increasing inflammation and sensitivity ***(Van Smeden et al., 2014)***.

▪ **Risk factors for AD flares:**

Atopic dermatitis flares can be triggered by several factors for example a moist environment, burns, high stress, anxiety, food allergies, history of alternative allergies or exposure to chemicals and metals. Complicating the risk factors for flares is that not everyone with AD will have the same triggers, so people with the disorder will have to keep track of their particular sensitivities.

Identifying triggers can be tricky, for example, sometimes there is a delay between eating a certain food and seeing a resulting flare-up ***(Tsakok et al., 2016)***.

Foods, chemicals and aeroallergens may play a role in the pathogenesis and exacerbation of AD. However, the exact roles of aeroallergens and food allergy are controversial because of limitations of the in vitro radioallergosorbent test (RAST) and skin prick test. Both tests have a nearly 90% negative predictive value for AD, but their positive predictive value is less than 50% because of the frequent false-positive results. Induction of bleeding, irritant reaction or nonspecific enhancement through axon reflex from nearby strong reaction, may all possibly lead to false-positive results. Therefore, it is important to place the test at least 2cm apart ***(Jamal, 2007)***.Placebo-controlled, food challenge studies have demonstrated that food allergens can induce eczematoid skin rashes in nearly 40% of children with moderate to severe AD. In a subset of these patients, urticarial reactions, or non-cutaneous symptoms, are elicited, which can trigger the itch-scratch cycle that flares this skin condition. Children with food allergies generally have positive immediate skin tests or serum IgE directed to various foods, particularly eggs, milk, wheat, soy, and peanuts. Food allergen–specific T cells have been cloned from the skin lesions of patients with AD, providing direct evidence that foods can contribute to skin inflammation ***(Helby et al., 2017).***

Exposure to aeroallergens such as pollens, molds, mites and animal dander appears to play an important role in AD flare in some patients with atopic dermatitis. Substantial clinical improvement may occur when these patients are removed from environments that contain the allergens to which they react ***(Walter et al., 2018)***.

Microbes like *S. aureus* also play a role in triggering flares of AD patients. Most patients with AD are colonized with *S. aureus* and suffer relapses of their skin disease following overgrowth of this organism ***(Helby et al., 2017)***. The magnitude of *S. aureus* in AD is supported by the observation that, in patients with secondary infection of *S. aureus*, treatment with a combination of anti-staphylococcal antibiotics and topical corticosteroids results in greater clinical improvement than treatment with topical corticosteroids alone ***(Helby et al., 2017)***.

One strategy by which *S. aureus* exacerbates AD is by secreting toxins called superantigens, which stimulate activation of T cells and macrophages. Most AD patients make specific IgE antibodies directed against staphylococcal superantigens ***(Ahn, 2014)***, and these IgE anti-superantigens correlate with skin disease severity. Another complication in the treatment of AD flares is that these toxic superantigens also induce corticosteroid resistance, suggesting that several mechanisms exist by which superantigens increase AD severity ***(Simpson et al., 2017)***.

Phosphodiesterase-4 enzyme

Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are key second messengers present in most cells and animal species. These cyclic nucleotides are implicated in numerous cellular processes initiated by the actions of hormones, neurotransmitters, chemokines and cytokines ***(Gorshkov, 2016)***.

The formation of cAMP and cGMP is regulated by adenylate cyclase and guanylate cyclase, respectively, while the degradation of these nucleotides occurs via phosphodiesterase (PDE) enzymes. PDE enzymes were first discovered 50 years ago shortly after the initial detection of cAMP. They are a super-family of enzymes that catalyze the hydrolysis of the cyclic phosphate bond of cAMP and cGMP to their inactive mononucleotides ***(Azevedo et al., 2013)***.

The cAMP signaling network is demonstrated in (Figure 4). Extracellular ligands such as hormones or neurotransmitters activate G protein-coupled receptors (GPCRs) such as the β-adrenergic receptor, which in turn trigger adenylate cyclase, a transmembrane protein to convert ATP to cAMP within the cell ***(Beavo and Brunton, 2002; Cooperet al., 2003; Conti et al., 2007; Houslay, 2010)***. An increased level of cAMP causes the

activation of effector proteins, mainly, protein kinase A (PKA) and exchange proteins activated by cAMP (EPAC). The phosphorylation of various proteins by PKA initiates a group of physiological responses. The signaling pathway involving cGMP is compared to the cAMP network described above ***(Yan et al., 2016)***.

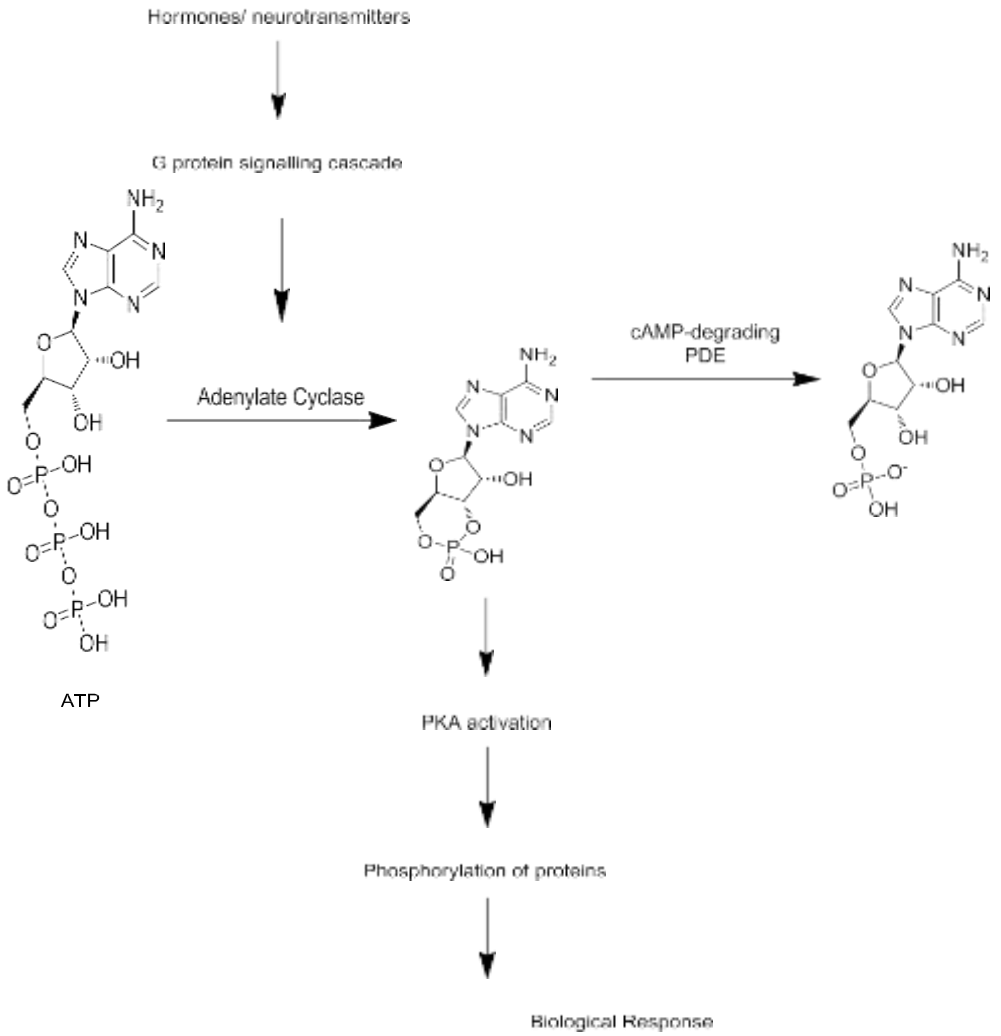

Figure (4): The cAMP signaling network ***(Houslay, 2010)***.

There are currently 11 distinct families of PDEs that have been identified and are numbered 1 – 11 ***(Francis et al., 2011; Keravis and Lugnier, 2012)***.

The family members are classified by their differences in sequence, substrate specificity, kinetic properties, and modes of regulation, intracellular localization and cellular expression as well as response to known inhibitors ***(Fasshauer and Blüher, 2015; Zhong et al., 2015)***. Each of the PDE families has a substrate preference for particular cyclic nucleotides. The PDE-4, 7, and 8 families specifically hydrolyze cAMP. PDE- 5, 6 and 9 favor the hydrolysis of cGMP. PDE- 1, 2, 3, 10 and 11 have a dual specificity for both cAMP and cGMP (Figure 5).

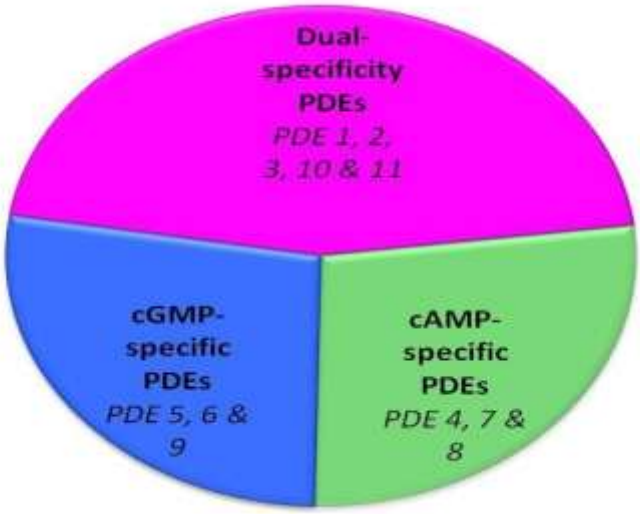

Figure (5): Mammalian PDE families grouped according to nucleotide specificity ***(Keravis and Lugnier, 2012)***.

The families are derived from 21 different genes. Most of them include more than one gene product ***(Maurice et al., 2014; Keravis and Lugnier, 2012)***.

For example, the PDE-1 family has three different subtypes PDE-1A, PDE-1B and PDE-1C ***(Azevedo et al., 2013; Rothenbuhler et al., 2012)***.

Alternate splicing of mRNA gives rise to different PDE isoforms with more than 100 subtypes. For example, there are two isoforms termed PDE-1B1 and PDE-1B2 for the PDE-1B subtype ***(Ahmad et al., 2015)***. The expression of PDE-1, PDE-2, PDE-3 and PDE-4 is widespread in many tissues; however, others are more limited ***(Francis et al., 2011)***. Many PDE isoforms have different patterns of expression in tissues and are involved in varying physiological responses and pathological processes ***(Sokolowska et al., 2015)***. Targeting of PDE subtypes and isoforms for the discovery of subtype selective inhibitors may help to decrease the unwanted side effects ***(Sutcliffe et al., 2014)***. PDE enzymes inhibitors block the degradation of cAMP and cGMP, thereby increasing their levels within the cell. By doing so, a range of physiological responses emerges ***(Haase and Rink, 2014)***.

Phosphodiesterase-4 enzymes (PDE4)

As PDE-4 enzymes are widely distributed in different cell types and tissues including immune and inflammatory cells (e.g., leukocytes), airway, vascular, smooth muscle and the brain. This makes them an attractive target for therapeutic intervention ***(Houslay and Adams, 2003; Knott et al., 2017)***. There are four enzyme subfamilies within the PDE-4 family known as PDE-4A, PDE-4B, PDE-4C and PDE-4D. The PDE-4 family contains close to 30 different isoforms, the most of any other PDE family ***(Houslay et al., 2007; Houslay, 2010; Maurice et al., 2014; Eskandari et al., 2015).*** PDE-4C has the most restricted expression of the PDE-4 subtypes with localization in the testes, skeletal muscle, lung, and cerebellum of the human brain ***(McKenna and Muller,2007; Jin et al., 2012).*** PDE-4A, PDE-4B and PDE-4D, in contrast, are widely distributed in immune and inflammatory cells including eosinophils, neutrophils, basophils, macrophages, monocytes, and lymphocytes ***(Bäumer et al., 2006; Wittmann and Helliwell, 2013)***.

In these inflammatory and immune cells, the increase in intracellular cAMP levels elicits inhibition of their activities including cytokine production, chemotaxis, cytotoxicity and cell aggregation ***(Almatary et al., 2018)***.

PDE-4 enzymes have been extensively studied previously and PDE-4 selective inhibitors are still

being actively pursued as they have potential therapeutic benefit in a wide range of major diseases. The diseases for which PDE-4 inhibition can treat comprise asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, multiple sclerosis (MS), diabetes mellitus, Crohn's disease, cancer, Alzheimer's disease, mild cognitive impairment, Parkinson's disease, Huntington's disease, schizophrenia and depression ***(Diamant and Spina, 2011; Pagès et al., 2009; Castro et al., 2005; Salari-Sharif and Abdollahi, 2010).***

5- Conclusion:

Atopic dermatitis is a complex disease caused by skin barrier dysfunction and immune dysregulation that involves many inflammatory cytokines. The limited topical treatments for patients with AD have led to development of novel non steroidal targeted therapies. PDE4 plays a role in the regulation of the inflammatory cascade associated with AD inflammation, making it a desirable target of drug therapy. PDE4 inhibitors have a unique mechanism that differs from the mechanisms of TCSs and TCIs, and they affect a broad range of cytokines involved in AD. One topical PDE4 inhibitor, crisaborole, has been approved in the United States for the treatment of AD, while several other agents are currently in clinical development. The mechanism of action of crisaborole will be further characterized in a study that is underway to evaluate the efficacy and changes in key skin biomarkers in patients with mild to moderate AD. Overall, evidence suggests that targeting of PDE4 may be a safe and effective approach to the management of AD. A recent review provides practical recommendations to help clinicians incorporate crisaborole into the treatment armamentarium for AD.

Conflict of interest

There is no conflict in this review.

Authors' contribution

All authors contributed to the writing and revising for intellectual content of the manuscript and approved the final version.

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