ANTIHISTAMINIC ACTIVITY MODELS

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ABSTRACT

Histamine is referred to as common allergic reactions and symptoms. Most of them are compared to histamine intolerance. Some common responses involved with this intolerance may vary but include headaches or migraines, nasal congestion or sinus problems, fatigue, hives, digestive problems, irregular menstrual cycle, nausea, and vomiting. Histamine is derived from a natural amino acid, S-histidine, through the histidine decarboxylase/ aromatic decarboxylase catalysis. Histamine is the compound that the mast cell generates for the immune response. Histamine promotes gastrointestinal secretion and induces capillary dilation, bronchial smooth muscle constriction, and reduced blood pressure. Antihistamines are medicinal products to treat allergic rhinitis and allergies. This includes the *in vitro* animal model and *in-vivo* tissue preparation antihistaminic activity. Animal models are significant instruments for understanding the pathological process of human illnesses in experimental medical science. Medicines associated with antihistamine include antiallergy, antivertigo, antimigraine, sedatives, antiemetic, etc. Elderly people are much more likely than youthful people to develop sleepiness from the use of antihistamines. The most common drugs used are cetirizine, levocetirizine, chlorpheniramine, diphenhydramine, loratadine, cimetidine, and fexofenadine. Animal models include histamine-induced bronchoconstriction, passive paw anaphylaxis, milk-induced leukocytosis and eosinophilia, clonidine, and haloperidol-induced catalepsy. While tissue models include isolated goat, and guinea-pig trachea chain preparation, as well as an isolated guinea pig, rat, mice ileum tissue preparation, and the dose-response curve of histamine, were plotted. The focus of the study had been on herbal plants and medicinal products, as they can effectively boost a variety of circumstances without significant adverse side effects. We can assess antihistaminic activity by using plant extracts or any synthetic drug.

Keywords: Histamine, Antihistaminic activity, Allergic rhinitis, Asthma, bronchoconstriction, Leukocytosis, Eosinophilia.

INTRODUCTION

Asthma is a common recurrent airway disease that is characterized by complex and persistent signs, reversible fluid restriction, and spasms. Allergy is one of the growing illnesses with various symptoms that influence humanity. Histamine is available in the mucosa of human nasal turbinates and lungs which is in charge of bronchoconstrictive reactions [1-4]. Histamine causes the manifestation of hypersensitive responses that, for the most part, include intense irritation by the H1 histamine receptor [5,6].

In every cell, there are four types of histamine receptors, that is, H1, H2, H3, and H4 [7]. Antihistamines (H1) structure a noteworthy helpful class of medications utilized in the treatment of an assortment of hypersensitive conditions such as rhinitis, urticaria, roughage fever, and even asthma [8,9]. Since their revelation and early improvement during the 1940s, histamine H1 receptor foes (antihistamines) have turned out to be one of the most broadly utilized classes of drugs for unfavorably susceptible issues [10]. More established original antihistamines show high restricting fondness for H1 receptors, yet a large number of these medications display restricting partiality for different classes of cell receptors, for example, the muscarinic cholinergic subtypes (M1M5) [11]. More up to this point, second-age antihistamines were created as moderately more particular histamine H1 receptor opponents than the initial operators, with some extent of limiting midway intervened impacts, as an example, sedation. Nonetheless, doubtlessly a portion of the fresher antihistamines is appropriate official to muscarinic receptors, just as to histamine H1 receptors in the cerebrum [12].

Another trademark highlight of the more established antihistamines is that they access the mind and tie to cell receptors within the central nervous system (CNS), causing sedation and disabled psychomotor execution [13]. The old-style antihistamines are linked to localized infection symptoms [14,15]. Histamine is one of the most prevalent inflammatory mediators; it triggers symptoms of allergic reactions, most of which involve severe H1 histamine-mediated inflammation [16,17]. The histamine H1 receptor is predominantly found in endothelial cells, soft muscle tissue, and neuro and adds to dilatation of blood vessels, enhanced capillary permeability, and cellular level pressure, thus causing increased intracellular calcium ($Ca2+$) and nitric oxide (NO) output at the molecular level [18-20].

MODELS FOR SCREENING OF ANTIHISTAMINIC ACTIVITY

In-vivo model/animal model
1. Histamine-induced bronchoconstriction in guinea pigs/mice/rats.
2. Passive paw anaphylaxis in rats/guinea pig/mice.
3. Milk-induced leukocytosis in mice.
4. Milk-induced eosinophilia in mice.
5. Clonidine-induced catalepsy in mice.
6. Haloperidol-induced catalepsy in mice.

In-vitro model/tissue model
1. Isolated goat trachea chain preparation.
2. Isolated guinea pig trachea chain preparation.
3. Guinea pig ileum tissue preparation.
4. Rat/mice ileum tissue preparation.

IN-VIVO MODEL/ANIMAL MODEL

1. Histamine-induced bronchoconstriction in guinea pigs/mice/rats
Animals were split into eight groups (n=6), the control group provided distilled water and a single extract dose was offered to other groups (75, 150, 200, 300, 600, and 1200 mg/kg p.o.). chlorprheniramine maleate (2 mg/kg) serve as a positive control. Pre- and post-medication treatment, each animal was kept within the histamine chamber and subjected to 0.2% histamine aerosol. The pre-convulsive

period (PCT) was calculated from the moment of initiation to the start of dyspnoea, contributing to the appearance of pre-convulsive dyspnoea within a min.

The percentage of protection offered by PCT drugs was determined for each dosage and positive control. The percentage protection was calculated using the formula below [21-31].

Percentage protection = (1 – T1/T2) × 100

Where T1 = PCT average before test drug administration and

T2 = PCT average after test drug administration

2. Passive paw anaphylaxis in rats/guinea pig/mice

On days 1, 3, and 5, animals got subcutaneously 100 μg of egg white. Blood was gathered from the retro-orbital plexus and centrifuged to isolate serum on the 10th day of sensitization. It was entitled to clot the gathered blood and at 1500 rpm the serum was divided by centrifugation. Animals in eight groups (n=6) were divided. The saline solution got by the control group and other groups were given a singular concentrate portion of 85, 175, 250, 350, 700, and 1400 mg/kg p.o. Dexamethasone (0.27 mg/kg p.o.) was utilized as a standard. Animals were sensitized with serum into the left hind paw before medication therapy. The right hind paw got the same normal saline solution quantity. The animals were examined with 10 μg of egg white in 0.1 ml of normal saline solution in left paw 1-h post-administration of the study drug and the paw expansion using a plethysmometer was assessed. Following 24 h, the level of edema restraint was determined to utilize the equation underneath [32-34],

Inhibition rate = [1 – (T/C)] 100

T – Average relative difference in paw volume (test group).

C – Average relative difference in paw volume (control group).

3. Milk-induced leukocytosis in mice

Mice (Swiss Albino) were split into six categories with each category containing six mice. Blood samples were obtained using pentobarbital sodium (i.p.), using RO (retro-orbital) vein under sedation. Class 1 served as normal control, Class 2 that received milk served as an intoxicant, Class 3 received standard as dexamethasone, and Class 4 to Class 6 received extract dose in low, moderate, and high dose. All classes got boiled and cooled milk infusion in the dose of 4 ml/kg s.c. after 30 min of drug treatment, excluding the normal control group.

Total leukocyte counts were conducted in each class before test compound administration and 24 h after milk infusion.

Calculate the change in total leukocytes count pre and post 24 h drug administration (Table 1) [35-39].

4. Milk-induced eosinophilia in mice

Mice (Swiss Albino) were split into six categories with each category containing six mice. Blood samples were obtained using pentobarbital sodium (i.p.), using RO (retro-orbital) vein under sedation. Class 1 served as normal control, Class 2 that received Milk served as an intoxicant, Class 3 received standard as dexamethasone, and Class 4 to Class 6 received extract dose in low, moderate, and high dose. All classes got boiled and cooled milk infusion in the dose of 4 ml/kg s.c. after 30 min of drug treatment, excluding the normal control group.

Total eosinophil counts were conducted in each class before test compound administration and 24 h after milk infusion.

Calculate the change in total leukocytes count pre and post 24 h drug administration (Table 1) [37,40-43].

5. Clonidine-induced catalepsy in mice

Mice (Swiss Albino) were split into five classes containing 5 mice each. Normal control (Class 1) provided saline solution (10 ml/kg) and other Class 3 to Class 5 received a single dosage of extract (100, 200, and 400 mg/kg body weight). Mice of Class 2 got standard dose chlorpheniramine maleate (antihistamine) (10 mg/kg, i.p.). One hour after intake of the drug, all the classes got clonidine (1 mg/kg s.c.), and the catalepsy period was determined at 15 min, 30 min, 60 min, 90 min, 120 min, 150 min, and 180 min (Table 2) [44,45].

6. Haloperidol-induced catalepsy in mice

Mice (Swiss Albino) were split into five classes containing five mice each. Normal control (Class 1) provided saline solution (10 ml/kg) and other Class 3 to Class 5 received a single dosage of extract (100, 200, and 400 mg/kg body weight). Mice of Class 2 got standard dose chlorpheniramine maleate (antihistamine) (10 mg/kg, i.p.). One hour after intake of the drug, all the classes got haloperidol (1 mg/kg s.c.), and the catalepsy period was determined at 15 min, 30 min, 60 min, 90 min, 120 min, 150 min, and 180 min (Table 3) [22,46].

Bar test scoring

The bar test was used for catalepsy measurements. In the bar test, the animal's front paw was placed alternatively on a horizontal bar 3 cm above and 5 cm parallel to the foundation. The moment the mice removes its front paw from the bar were observed.

Table 1: Animal grouping for milk-induced leukocytosis and eosinophilia study [37,40-43]

Class	Test substance	Albino mice per group	Dose as required	Total
1	Normal saline	6	ml/kg	6
2	Milk	6	mg/kg	6
3	Milk+Dexamethasone	6	mg/kg	6
4	Milk+Extract (Low dose)	6	mg/kg	6
5	Milk+Extract (Moderate dose)	6	mg/kg	6
6	Milk+Extract (High dose)	6	mg/kg	6
Total animals required				36

Table 2: Animal grouping for clonidine-induced catalepsy study [44,45]

Class	Test substance	Albino mice per group	Dose as required	Total
1	Normal saline+clonidine	5	ml/kg	5
2	Standard+clonidine (chlorpheniramine maleate)	5	mg/kg	5
3	Extract+clonidine (LOW DOSE)	5	mg/kg	5
4	Extract+clonidine (medium dose)	5	mg/kg	5
5	Extract+clonidine (high Dose)	5	mg/kg	5
Total animal required				25

Table 3: Animal grouping for haloperidol-induced catalepsy study [22,46]

Class	Test substance	Albino mice per group	Dose as required	Total
1	Normal saline+haloperidol	5	ml/kg	5
2	Standard+haloperidol (chlorpheniramine maleate)	5	mg/kg	5
3	Extract+haloperidol (low dose)	5	mg/kg	5
4	Extract+haloperidol (medium dose)	5	mg/kg	5
5	Extract+haloperidol (high dose)	5	mg/kg	5
Total animal required				25

Catalepsy valuing was given as follows
- Step 1: The mice were removed from the house cage and placed on the table. If the mice did not move, a value of 0.5 was allocated when touched or softly pushed back.
- Step 2: The mice's front paws were alternatively put on a 3 cm long bar. If the mice did not correct the posture within 15 s, for each paw a value of 0.5 was added to the value of Step 1.
- Step 3: The mice's front paws were alternatively put on a 5 cm long bar, if the mice did not correct the posture within 15 s, on each paw a value of 1 was added to the value of Step 1 and 2.

Formula to calculate catalepsy value
Total value= 0.5 + [0.5 × time (in s) of front right paw on 3 cm long bar] + [0.5 × time (in s) of front left paw on 3 cm long bar] + [1 × time (in s) of front right paw on 5 cm long bar] + [1 × time (in s) of front left paw on 5 cm long bar].

***IN-VITRO* MODEL**

1. Isolated goat trachea chain preparation
From the adult goat, isolated tracheal tissue was acquired instantly after the animals were slaughtered. Tracheal was cut into separate pieces and sequentially connected to form a chain. In Krebs bathwater, trachea was suspended and constantly aerated at 37±0.5°C. At one end of the prepared tracheal chain was connected to the s-shaped aerator pipe and another end connected to an isotonic frontal writing lever. The histamine dose-response curve (DRC) was traced on the kymographic sheet that is mounted on a revolving drum.

A graphic of the largest percentage of contractile responses to histamine ordinate and abscissa concentration was considered for the screening of histamine DRC in the lack and existence of drug extract [47-55].

2. Isolated guinea pig trachea chain preparation
From the guinea pig, isolated tracheal tissue was acquired instantly after the animals were slaughtered. The trachea was cut into separate pieces and sequentially connected to form a chain. In Krebs bathwater, trachea was suspended and constantly aerated at 37±0.5°C. At one end of the prepared tracheal chain was connected to the s-shaped aerator pipe and another end connected to an isotonic frontal writing lever. The histamine dose-response curve (DRC) was traced on the kymographic sheet that is mounted on a revolving drum.

A graphic of the largest percentage of contractile responses to histamine ordinate and abscissa concentration was considered for the screening of histamine DRC in the lack and existence of drug extract [55-58].

3. Guinea pig/rabbit ileum tissue preparation
The guinea pigs/rabbit which were fasted overnight were sacrificed and the ileum was put in an organ bath with a Tyrode solvent that was constantly aerated at 37±0.5°C. The histamine dose-response curve was carried out in the plain Tyrode solvent and in the extract-containing Tyrode solvent. The largest percentage of contractile responses in the lack and existence of the extract was intended to generate the histamine dose-response curve [59-61].

4. Rat/mice ileum tissue preparation
The rat/mice which were fasted overnight were sacrificed and the ileum was put in an organ bath with a Tyrode solvent that was constantly aerated at 37±0.5°C. The histamine dose-response curve was carried out in the plain Tyrode solvent and in the extract-containing Tyrode solvent. The largest percentage of contractile responses in the lack and existence of the extract was intended to generate the histamine dose-response curve [59,62-66].

Tissue preparation
Before 1 day of the start of the study, the animals were dieted overnight with free water exposure. Animals had been killed humanly by ether under sedation. The cervical dislocation slaughtered animals were used. About 1 cm from the ileocaecal junction, a 3 cm portion of the ileum was surgically removed. As described earlier, the transverse tissue sheet had been removed. Nearly 1.5 cm long strips were set in 5 ml organ water containing Krebs-Henseleit arrangement with 95% O2 and 5% CO_2 and held at 37°C.

Tissue was fixed, with the aid of two tight loops. At one end of the prepared tracheal chain was connected to the s-shaped aerator pipe and another end connected to an isotonic frontal writing lever. Before the procedures began, the tissue strips were balanced for 45 min under resting stress of 1 g. Tissue responses, that is, histamine dose-response curve, had been traced on kymographic paper [67].

CONCLUSION

Asthma is an immune-involved inflammatory disease. Treatment includes many factors that are capable of managing asthma. The current research was scheduled to assess the effect of the extract on different elements of asthma, such as bronchoconstriction, eosinophilia, and inflammation-related allergy using different animal models *in vitro* and *in vivo*.

Recently, as innovative clinical strategies for the research of anti-histaminic disease and its related disorders, many herbal plants and medicinal items have received research interest because they can effectively improve a variety of circumstances without severe adverse side effects.

AUTHORS' CONTRIBUTIONS

We declare that this work was done by the authors named in this article and all liabilities about claims relating to the content of this article will be borne by the authors. Ms. Priya Gupta, Ms. Shalaka Kadam, Mr. Salman Kapadia, and Ms. Falak Bamne collected the data and analyzed the data. Dr. (Mrs.) Vanita Kanase proofread the whole manuscript and suggested the necessary changes, and helps in designing the manuscript.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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