European Journal of Pharmacology 788 (2016) 152–159

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Pulmonary, gastrointestinal and urogenital pharmacology

Role of selective blocking of bradykinin receptor subtypes in attenuating allergic airway inflammation in guinea pigs

Mohamed M. El-Kady [a,*], Zarif I. Girgis [a], Eman A. Abd El-Rasheed [a], Olfat Shaker [b], Magdy I. Attallah [a], Ahmed A. Soliman [c]

[a] Department of Medical Pharmacology, Faculty of Medicine, Cairo University, 11559, Egypt
[b] Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, 11559, Egypt
[c] Department of Pathology, Faculty of Medicine, Cairo University, 11559, Egypt

ARTICLE INFO

Article history:
Received 3 February 2016
Received in revised form
10 June 2016
Accepted 15 June 2016
Available online 16 June 2016

Keywords:
Bradykinin
R-715
Icatibant
Airway hyperresponsiveness
Bronchoalveolar lavage
Asthma

ABSTRACT

The present study was designed to evaluate the potential role of bradykinin antagonists (R-715; bradykinin B_1 receptor antagonist and icatibant; bradykinin B_2 receptor antagonist) in treatment of allergic airway inflammation in comparison to dexamethasone and montelukast. R-715 as dexamethasone significantly decreased peribronchial leukocyte infiltration, bronchoalveolar lavage fluid (BALF) albumin and interleukin 1β as well as serum OVA-specific IgE level. Also, R-715 like montelukast significantly decreased BALF cell count (total and eosinophils). Icatibant showed negative results. The current findings suggest that selective bradykinin B_1 receptor antagonists may have the therapeutic potential for the treatment of allergic airway inflammation.

1. Introduction

Bronchial asthma is a complex disease or a syndrome characterized clinically by reversible bronchial obstruction (Haahtela, 2009). Asthma affects more than 334 million people worldwide (GAR, 2014).

Bradykinin and its metabolite des-Arg9-bradykinin mediate their effects through cell membrane attached receptors called bradykinin receptors that belong to the G protein–coupled family of receptors. Two bradykinin receptors are well characterized; bradykinin B_1 and B_2 receptors. The former is up-regulated in many inflammatory conditions, while the latter is constitutively expressed (Marceau and Regoli, 2004).

Bradykinin first isolated by Rocha e Silva, Beraldo, and Rosenfeld, is a "slow" smooth-muscle-contracting substance, derived from plasma globulins by the proteolytic action of trypsin (Ambache and Silva, 1951).

R-715 is very highly selective antagonist for bradykinin B_1 receptors (Marceau et al., 1998). R-715, described initially in 1996 by Gobeil et al. is a synthetic peptide (Ac-Lys-[D-betaNal7,lle8] desArg9-bradykinin) that is partially resistant to degradation by angiotensin converting enzyme (Gobeil et al., 1996). R-715 reversed zymosan-induced hyperalgesia in a rat model of localized inflammatory hyperalgesia (Bélichard et al., 2000). Twice daily administration of R-715 for 7 days, significantly attenuated the hyperalgesic effect developed in streptozotocin-diabetic mice (Gabra and Sirois, 2003). Also, R-715 decreased cellular migration at the inflammatory site, in carrageenan-induced mouse pleurisy (Costa et al., 2006), reduced diabetes-induced Evans blue extravasation in diabetic rat retina (Abdouh et al., 2008) and significantly inhibited the capsaicin-induced ear oedema in mice when administered 15 min before the application of capsaicin (Pietrovski et al., 2009).

Icatibant is a potent synthetic selective bradykinin B_2 receptor antagonist. Icatibant, distantly related to the first peptide antagonists of bradykinin B_2 receptors described by Vavrek and Stewart (1985), incorporates several non-natural residues that confer rigidity to its backbone and resistance to peptidases (Hock et al., 1991; Wirth et al., 1991). It is stable and not degraded by bradykinin-cleaving enzymes such as carboxypeptidase N (or kininase I) and angiotensin-converting enzyme (or kininase II) (Bas et al., 2010). Icatibant is a 10–amino acid peptide prepared by direct biosynthesis (Frank and Jiang, 2008). Icatibant is administered by subcutaneous injection at a dose of 30 mg and was licensed in the

* Corresponding author.
E-mail addresses: mahammad_elkady@yahoo.com, mahammad_elkady@cu.edu.eg (M.M. El-Kady), zarifisaak@ymail.com, zarifisaak@kasralainy.edu.eg (Z.I. Girgis), dreman58@hotmail.com (E.A. Abd El-Rasheed), olfatshaker@yahoo.com (O. Shaker), drmagdyishak@yahoo.com (M.I. Attallah), drahmedsoliman@yahoo.com (A.A. Soliman).

http://dx.doi.org/10.1016/j.ejphar.2016.06.024
0014-2999/

United States in August 2011 for physician- or patient-administered treatment of acute attacks in adults 18 years and older with Hereditary Angioedema (Riedl, 2012). Also, administration of icatibant was followed by rapid relief of symptoms in patients with angiotensin-converting enzyme inhibitor induced angioedema (Bas et al., 2010). The plasma half-life of icatibant is two to 4 h. It is degraded by peptidases, and the degradation products are excreted via the kidneys (Bork et al., 2007). Icatibant has been associated with minor cutaneous reactions at the site of injection. Little is known about the long-term effect of bradykinin inhibition (Frank and Jiang, 2008).

Taken together, the present study was designed to evaluate the potential role of bradykinin antagonists (R-715 and icatibant) in treatment of allergic airway inflammation.

2. Materials and methods

2.1. Animals

Experiments in this study were carried out on male English short hair tricolor guinea pigs (weight 300–350 g) that were housed and placed under a 12 h light/dark cycle. Animals had free access to food and water throughout the experiments. All experiments and procedures were in accordance with the local regulations of Cairo University as well as the eighth edition of the Guide for the Care and Use of Laboratory Animals.

2.2. Drugs and chemicals

The following drugs were used: R-715 (Toccris, UK), icatibant (Toccris, UK), dexamethasone as Fortecortin® ampoules (Sigma-Tec Pharmaceutical Industries S.A.E.), montelukast as Singulair® tablets (Global Napi Pharmaceuticals-Egypt), acetylcholine (MP Biomedicals, USA), mepyramine maleate (MP Biomedicals, USA), urethane (Sigma-Aldrich, Germany) and succinylcholine as Succinylcholine Chloride® ampoules (Misr Co. for Pharm. Ind. S.A.E.). The following chemicals were used: ovalbumin (Bio Basic®, Canada) and aluminum hydroxide containing adjuvant (Imject® Alum, Pierce Biotechnology, USA).

2.3. Exposure box

A transparent box assembled from Perspex sheets, that measure 50 cm × 30 cm × 30 cm as length, width and depth (or height) respectively, was made to in order to expose animals to ovalbumin (OVA) aerosol during sensitization and challenge protocols. The box has been equally divided into 3 separate cells by perpendicular holed Perspex sheets to accommodate just two animals in each. As a means to adequately ventilate the box, inflow and outflow air ports were installed and fresh air was delivered by air compressor (Norditalia Elettromedicali, Italy, Model: Air Family). Two inlets in one sidewall were used to deliver OVA aerosol generated by the ultrasonic nebulizer (Shanghai MedEco Industry Co., Ltd. China, Model W002).

2.4. Animal sensitization and allergen challenge

Guinea pigs were sensitized as previously described with minor modifications. Initially, 100 μg OVA (200 μl of 0.05% solution) adsorbed to 100 μl of Imject® Alum was intraperitoneally injected. One week later, the animals were exposed to an aerosol of 0.5% OVA solution for 5 min in the aforementioned exposure box. The ultrasonic nebulizer was set to produce a continuous aerosol (particle size of 1–5 μm) at a rate of 2 ml/min. Bias flow in the chamber was 11 l/min, driven by an air compressor. This was repeated a total of three times at one-week intervals as a booster (Fig. 1). One week after the final booster (on day 35), the animals were challenged with aerosolized 0.5% OVA solution for 60 min. To avoid anaphylactic shock, animals were pretreated with mepyramine (10 mg/kg, i.p.) 30 min before each OVA exposure (Bergren, 2001; Mukaiyama et al., 2004).

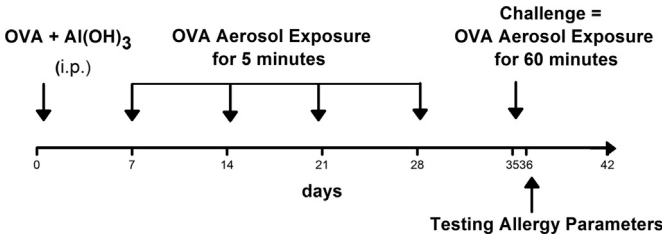

Fig. 1. Time line of asthma induction and allergen challenge.

2.5. Experimental groups

Animals were randomly allocated to the following groups (6 animals each). Negative control groups were represented by nonsensitized nontreated group, OVA-sensitized saline-challenged (60 min) nontreated (O/S-NT) and OVA-sensitized OVA-challenged nontreated (O/O-NT). Two sensitized groups were treated with R-715 and icatibant. R-715 was dissolved in distilled water and given at a dose of 1.14 mg/kg body weight (extrapolated from rats and modified). It was injected intraperitoneally 30 min before OVA-challenge, 3 h after challenge and on the following day 2 h before testing airway reactivity (Abdouh et al., 2008). Icatibant was dissolved in distilled water and given at a dose of 130 μg/kg. It was injected intraperitoneally 30 min before challenge, 3 h after challenge and on the following day 2 h before testing airway reactivity (Ricciardolo et al., 1994). Two positive control groups were treated by dexamethasone and montelukast. Dexamethasone was given at a dose of 5 mg/kg. Dexamethasone was injected intraperitoneally a day before challenge, one h before challenge and on the following day 2 h before testing airway reactivity (Ozer et al., 2008). Montelukast was suspended in distilled water and was given at a dose of 5 mg/kg. Montelukast was administered by oral gavage (through a straight needle, 15 Gauge, 15 cm length with a blunt tip), a day before challenge, 2 h before challenge and on the following day two h before testing airway reactivity (Gobbato et al., 2012).

2.6. Determination of airway-hyperresponsiveness (AHR)

Airway resistance was measured according to the method of Konzett and Rossler (1940) with minor modifications. Briefly, Twenty-four hours after OVA last exposure (day 36), guinea pigs were anaesthetized with intraperitoneal administration of urethane (50% solution, 2 g/kg of body weight) (Plevkova et al., 2010). A tracheal cannula was connected to a small animal respirator (Searle BioScience, UK, Model: Miniature Ideal Pump). The animals were artificially ventilated with a constant volume respiration at a tidal air volume of 10 ml/kg and a frequency of 37 strokes/min (Muraki et al., 2009). The jugular vein was cannulated for intravenous injection of Ach (Takami and Tsukada, 1998). To eliminate spontaneous respiration, guinea pigs were treated with succinylcholine chloride (2.5 mg/kg, s.c.). After a stabilization period of 15 min, changes in the peak inflation pressure (PIP; mmHg) at constant airflow were measured using a pressure transducer connected to a side arm of the tracheal cannula at one end and to the computerized data acquisition system (Powerlab®, ADinstruments, Australia) at the other end (Eric et al., 2003). PIP was measured at baseline and following intravenous