CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1470637

Available online at: http://www.iajps.com Research Article

ANALYSIS OF USE OF NEUROPEPTIDES IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN PAKISTAN

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Abstract:

Introduction: *Many neuropeptides have recently been identified in human and animal airways. These peptides have potent effects on airway caliber, blood vessels, and secretions, raising the possibility that they may be involved in airway diseases such as asthma.* ***Objectives of the study:*** *The basic aim of the study is to analyze the use of neuropeptides in asthma and chronic obstructive pulmonary disease in Pakistan.* ***Methodology of the study:*** *This study was conducted at Children Hospital & Institute of Child Health, Multan during January 2018 to April 2018. This study was conducted with the permission of ethical committee of hospital. In this study we analyze the use of different neuropeptide drugs for asthma and chronic obstructive pulmonary disease.* ***Results:*** *Here we review a few select neuropeptides that have either been shown to impact or have the potential to impact the pathogenesis and progression of either asthma, COPD, or CF. Special emphasis is placed on neuropeptides that have not received much attention, and/or those that have been recently discovered.* ***Conclusion:*** *It is concluded that Neuropeptides continue to be a source of insight and complexity when it comes to airway disease.*

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Please cite this article in press Mehak Siddiqui et al., ***Analysis of Use of Neuropeptides in Asthma and Chronic Obstructive Pulmonary Disease in Pakistan.,*** *Indo Am. J. P. Sci, 2018; 05(10).*

INTRODUCTION:

Many neuropeptides have recently been identified in human and animal airways. These peptides have potent effects on airway caliber, blood vessels, and secretions, raising the possibility that they may be involved in airway diseases such as asthma. Vasoactive intestinal peptide and peptide histidine methionine are potent bronchodilators and may be neurotransmitters of non-adrenergic bronchodilator nerves [1]. In asthma, if these peptides are broken down more rapidly by enzymes from inflammatory cells, this might contribute to exaggerated bronchial responsiveness. Neuropeptides that are found in sensory nerves, such as substance P, neurokinin A, and calcitonin gene related peptide, have inflammatory effects and might also contribute to the pathology of asthma if released from sensory nerve endings by an axon reflex [2].

Neuropeptides, by definition, are peptides that are formed by the enzymatic processing of gene-encoded precursor molecules. They are produced, stored, and secreted upon demand via regulated secretory pathways. Due to different enzyme cleaving and processing of the precursor molecules, current neuropeptides are classified into families based upon the genes encoding those precursors. The molecules that fit this definition are called "classic neuropeptides". However, with increased interest and evolving research, new members are constantly emerging, and the definition continues to expand as new molecules that have some neuropeptide features, but lack others, are discovered [3]. Expression of precursor molecules occurs predominantly in neurons where they are stored in large granular vesicles in the cytoplasm and released upon stimulation. After their release, classical neuropeptides exert their specific actions upon a variety of target cells via G-protein coupled receptors. Their actions can be exerted on other neurons as modulators of signaling, or on non-neuronal cells as signaling molecules [4]. Therefore in many organs, neuropeptides can exert effects through direct innervation of the end organ, but also through non-synaptic contact and paracrine activity on neighboring cells. Additionally, more than one receptor type and different G-protein coupling of neuropeptide receptors in different tissues lead to variable effects of the same neuropeptides in different tissues/cell types. This also adds to the complexity observed in the effects of neuropeptides [5].

Many neuropeptides co-exist in the same neurons, where they influence production and secretion of one another, thus exerting a neuromodulatory role. Because of this, predicting the consequences of neuropeptide release and/or activation can be difficult. Moreover, in the lung, non-neuronal cells, known as neuroendocrine cells, synthesize and secrete neuropeptides. These cells add an additional layer of regulation and have recently gained interest in asthma and CF [6].

Objectives of the study

The basic aim of the study is to analyze the use of neuropeptides in asthma and chronic obstructive pulmonary disease in Pakistan.

METHODOLOGY OF THE STUDY:

This study was conducted at Children Hospital & Institute of Child Health, Multan during January 2018 to April 2018. This study was conducted with the permission of ethical committee of hospital. In this study we analyze the use of different neuropeptide drugs for asthma and chronic obstructive pulmonary disease. Asthma and COPD are common, chronic, and heterogeneous pulmonary diseases that have a significant impact on quality of life. Asthma is primarily viewed as an inflammatory disorder of the airways and often is diagnosed at young age. It is characterized by wheezing, cough, chest tightness and variable airflow limitation that is partially reversible. Key features of asthma include airway hyper reactivity, as well as alterations in the quantity and quality of airway mucus. Although inflammation is a cornerstone of asthma, several studies have shown that the nervous system plays a fundamental role in its pathogenesis.

Sample size determination

The sample size was calculated based on single sample size estimation. The value of p is taken considering 95% confidence interval, 5% margin of error and the value of p taken was 50% because there is no study conducted related with CKD associated factors.

Ethical consideration

This research project was approved by "Departmental Ethics and Research committee" of the hospital. The purpose of the study was explained to the study participants accordingly. Permission was obtained from hospitals research center and nephrology clinic.

Statistical analysis

The data of respiratory function were compared between the smoker and non-smoker groups using the independent t-test for normally distributed data or the Mann-Whitney U test for other distributions. Differences were considered statistically significant at $p<0.05$.

RESULTS:

Here we review a few select neuropeptides that have either been shown to impact or have the potential to impact the pathogenesis and progression of either asthma, COPD, or CF. Special emphasis is placed on neuropeptides that have not received much attention, and/or those that have been recently discovered. We summarize the involvement of these neuropeptides in mucus secretion in Table 1, and their effects on mucus secretion in asthma, COPD, and CF.

Table 1: General overview of neuropeptides and their effect on airway mucus secretion

Neuropeptide	General effect on mucus secretion
Calcitonin gene-related peptide (CGRP)	Induced small concentration-dependent increases in basal mucus volume, lysozyme and albumin outputs from in vitro ferret trachea culture at baseline
	Stimulated goblet cell hyperplasia when co-administered with GABA
	Stimulate goblet cell secretion
Bombesins	GRP-27 induced dose-dependent increase of respiratory glycoconjugate secretion in feline tracheal organ culture
	Bombesin receptor-activated protein BRAP (a downstream protein from the activation of the orphan bombesin receptor subtype-3) regulates neutrophil elastase-induced muc5AC hypersecretion in human bronchial epithelial cell line
Substance P (SubP)	Stimulates human airway submucosal gland secretion
	Increases goblet cell secretion
Granins	Secretoneurin induced Muc5AC hypersecretion in a dose- and time-dependent manner in human HBE16 bronchial epithelial cell line
Vasoactive intestinal peptide (VIP)	Stimulates mucus secretion in ferret trachea
	Knockout of the VIP receptor (VPAC2) in a murine model of Aspergillus antigen-induced asthma lead to a marked enhancement of MUC5AC mRNA and an associated increase in goblet cells in the lungs
Neuropeptide Y	Modulates mucus output from airway submucosal glands

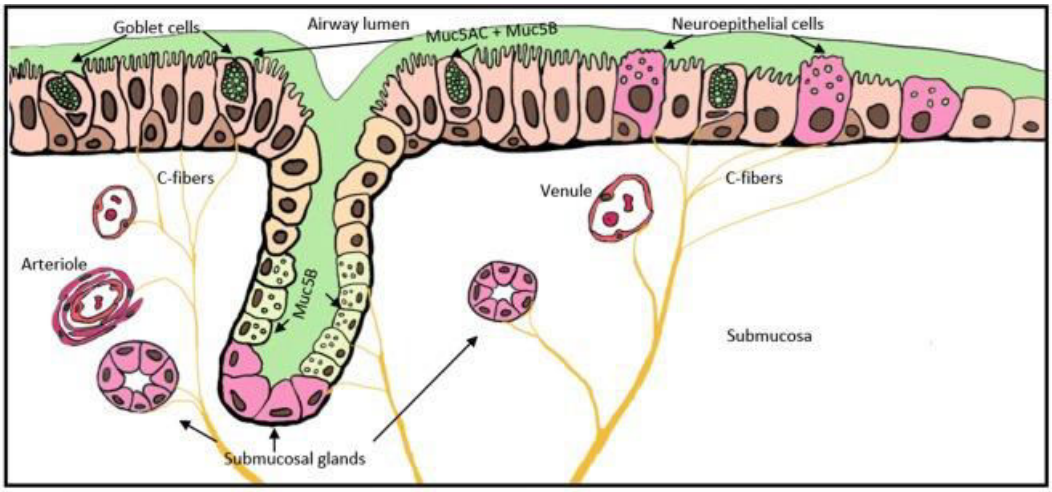

Fig 1: Summary of the effects of neuropeptides on mucus secretion from submucosal glands and goblet cells. Diagram shows model of airway.

DISCUSSION:

In asthmatic airways, mucus content positively correlated with SubP expression; NK1 receptors were also elevated with strongest expression detected on goblet cells. The authors of that study concluded that neurogenic mechanisms contributed to asthma[6]. Consistent with that, Tomaki and colleagues found that SubP levels in sputum correlated with airway obstruction in asthma. In an experimental murine model of allergic asthma, increased bronchoalveolar lavage fluid concentrations of SubP were associated with induction of muc5AC mRNA, further suggesting a potential pathogenic role for tachykinins in asthma. Other studies have found a positive correlation between muc5AC and NKA protein expression in the sputum of asthmatics. There are currently no studies available that provide information regarding the role of NKB in regulating muc5AC or muc5B expression, nor of SubP or NKA in the regulation of muc5B, in asthma[7].

Although SubP stimulates gland secretion in "normal" submucosal glands, reports suggest that it is ineffective in people with CF[8]. This finding has been reproduced in pigs with CF. An implication from those studies was that defective responses to SubP might contribute to airway pathology in CF[9]. Given that glandular secretion in response to SubP is defective in CF, a speculation is that SubP-mediated secretion in CF might be associated with enhanced muc5AC to muc5B secretion ratios, effectively mimicking asthma. Moreover, in contrast to asthma and COPD, where enhanced SubP and/or tachykinin signaling is potentially pathogenic, a decrease in SubP-mediated secretion in CF might be of detriment[10].

CONCLUSION:

It is concluded that Neuropeptides continue to be a source of insight and complexity when it comes to airway disease. Although significant progress has been made in understanding the contributions of some neuropeptides to asthma, COPD, and CF, their specific contributions to mucus obstruction and/or hyper secretion is, in many ways, unknown.

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