NEUROASTHMA

Essay

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SUMMARY

Asthma is a chronic disorder characterized by airway inflammation, reversible airway obstruction and AHR; in which eosinophils, MCs, neutrophils, cytokines and mediators play important roles in its pathogenesis. These different inflammatory cells are involved in asthma, although the precise role of each cell type is not yet certain. Many different mediators (such as histamine, PG, LTs and kinins) have been implicated in asthma.

Researchers suggest that some genetic variants may only cause asthma when they are combined with specific environmental exposures, and otherwise may not be risk factors for asthma.

The aim of this work was to present a new vision of asthma as it is a neurogenic disease (Neuroasthma) and to study scientific background of effective use of anticonvulsants for pharmacotherapy of bronchial asthma.

Many different neuromediators have been implicated in asthma pathogenesis:

. Neurotrophins (NTs) are a family of proteins that induce the survival, development and function of neurons. NTs, such as NGF, BDNF, NT-3 and NT-4, exert their

function by binding two different receptor subtypes. The low-affinity pan-neurotrophin receptor $p75^{NTR}$ and the tropomyosin receptor kinases *(Trks*) TrkA, TrkB and TrkC. NTs promote airway inflammation by interaction with different immune cell subtypes and contribute to an altered neuronal control of the airways.

. Several peptides have been demonstrated in mammalian lung. Some of them are present in the innervation of the mucosa, submucosa, smooth muscle and blood vessels and are called neuropeptides. Release of neuropeptides, including tachykinins and CGRP, from sensory nerves via an axon or local reflex causes ASM contraction and modulates immune cell functions, which then leads to neurogenic inflammation.

. Opioid alkaloids and peptides, such as morphine and the endogenous opioid peptides, modulate the function of lymphocytes and other cells involved in host defense and immunity. Apart from the presence of the classical opioids and their receptors in the lung and their functional role, a new group of peptides such as nociceptin and endomorphins has been characterized in the airways.

. GABA is the major inhibitory neurotransmitter in the mammalian central nervous system and exerts its

actions via both ionotropic ($GABA_A$/$GABA_C$) channels and metabotropic ($GABA_B$) receptors. $GABA_A$ channels and $GABA_B$ receptors have been functionally identified on peripheral nerves in the lung. Many studies have revealed complex GABA signaling systems in the AECs, ASM and inflammatory cells**.**

Bronchial asthma is mainly paroxysmal inflammatory disease and neurogenic inflammation may play important role in asthma mechanisms. Airways inflammation during asthma also is more neurogenic than immune process. The role of allergies is very important during asthma, but allergies may be only an initial trigger factor for neurogenic development of asthma as a chronic disease.

So, bronchial asthma may be a neurogenic paroxysmal inflammatory disease (*Neuroasthma*) with the complex pathogenic mechanism, including two levels of components: 1) multiple trigger components and 2) central neurogenic generator component.

Until today, management of bronchial asthma was held in **two** main directions:

1) Modification of factors inducing allergic reaction and interference on the certain stages of allergic reaction.

2) Interference with peripheral bronchial receptors. Both these directions do finally affect the trigger factors.

Considering the bronchial asthma as a neurogenic paroxysmal and inflammatory disease having certain similar pathogenic mechanisms with epilepsy, migraine, trigeminal neuralgia and breath-holding spells, a **3rd** direction in the management of bronchial asthma is suggested: application of anticonvulsive agents for the control of activity of generator neurogenic mechanisms of bronchial asthma.

This kind of medication has been successfully applied in many trials: in more than 70% of patients with asthma some AEDs induced complete and stable remission. This new approach leads to the prevention of asthmatic attacks and opens up new perspectives for the management of this disease.

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INTRODUCTION

Asthma is a chronic disorder characterized by airway inflammation, reversible airway obstruction and airway hyperresponsiveness; in which eosinophils, mast cells (MCs) and neutrophils play important roles in its pathogenesis ***(Kazuyuki and Makoto, 2011).***

Asthma is a problem worldwide with an estimated 300 million affected individuals. Annual worldwide deaths from asthma have been estimated at 250,000 and mortality does not appear to correlate well with prevalence ***(Masoli et al., 2004).***

Asthma prevalence and asthma deaths also differ by gender. Males are more likely to be diagnosed with asthma as children, but asthma is more likely to persist into adulthood in females ***(Osman et al., 2007).***

In an American study, it was found that there were 1.75 million asthma-related emergency department visits and 456,000 asthma hospitalizations. Asthma emergency visit and hospitalization rates were higher among females than males and among black than white persons ***(Akinbami et al., 2011).***

Several irritant stimuli (such as fog, sulfur dioxide, dust and cold air) provoke reflex bronchoconstriction by stimulating the sensory receptors in the airways. In both normal subjects and subjects with asthma, this physiological defense mechanism is able to provoke bronchoconstriction. However, the bronchoconstriction response in subjects with asthma develops at lower levels of stimulation and is more intense compared to that in normal subjects ***(Tai and Baraniuk, 2002).***

Many different inflammatory cells are involved in asthma, although the precise role of each cell type is not yet certain. It is evident that no single inflammatory cell is able to account for the complex pathophysiology of allergic disease, but some cells predominate in asthmatic inflammation ***(Barnes, 2002).***

Many different mediators have been implicated in asthma and they may have a variety of effects on the airways that could account for all of the pathological features of allergic diseases. Mediators (such as histamine, prostaglandins (PG), leukotrienes (LTs) and kinins) contract airway smooth muscle (ASM), increase microvascular leakage, increase airway mucus secretion and attract other inflammatory cells ***(Frieri, 2005).***

Many different neuromediators have been implicated in asthma pathogenesis, such as:

1) - **Neurotrophins (NTs)**, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin- 3 (NT-3) and NT-4, are a family of proteins that induce the survival ***(Hempstead, 2006)***, development, and function ***(Reichardt, 2006)*** of neurons. NTs promote airway inflammation by interaction with different immune cell subtypes and contribute to an altered neuronal control of the airways ***(Nassenstein et al., 2006).***

2) - **The sensory neuropeptides tachykinins**, such as substance P (SP), neurokinins A and B (NKA, NKB) and calcitonin gene-related peptide (CGRP) have been put forward as neurotransmitters of the local axon reflex. Release of neuropeptides from sensory nerves via an axon or local reflex causes ASM contraction and modulates immune cell functions, which then leads to neurogenic inflammation. This neurogenic inflammation may be initiated by activation of sensory nerves by inflammatory mediators and irritants ***(De Swert and Joos, 2006)***.

3) - **Opioid alkaloids and peptides**, such as morphine and the endogenous opioid peptides modulate the function of lymphocytes and other cells involved in host defense and

immunity. Opioid receptors are activated both by endogenously produced opioid peptides and by exogenously administered opiate compounds ***(Janecka et al., 2004; Waldhoer et al., 2004)***. Their localization to neurons projecting into airways suggested a possible role as regulators of neurogenic inflammation, bronchoconstriction and mucus secretion ***(Groneberg and Fischer, 2001).***

4) - **Gamma-Aminobutyric acid (GABA)** is the major inhibitory neurotransmitter in the mammalian central nervous system and exerts its actions via both ionotropic ($GABA_A$/$GABA_C$) channels and metabotropic ($GABA_B$) receptors. $GABA_A$ channels and $GABA_B$ receptors have been functionally identified on peripheral nerves in the lung ***(Mizuta et al., 2008).***

Until today, management of bronchial asthma was held in **two** main directions:

1) Modification of factors inducing allergic reaction and interference on the certain stages of allergic reaction.

2) Interference with peripheral bronchial receptors. Both these directions do finally affect the trigger factors.

Considering the bronchial asthma as a neurogenic paroxysmal and inflammatory disease having certain similar

pathogenic mechanisms with epilepsy, migraine, trigeminal neuralgia and breath-holding spells ***(Lomia et al, 2004; 2005; 2006)***, a **3rd** direction in the management of bronchial asthma is suggested: application of anticonvulsive agents for the control of activity of generator neurogenic mechanisms of bronchial asthma.

This new approach leads to the prevention of asthmatic attacks and opens up new perspectives for the management of this disease. This kind of medication has been successfully applied in many trials: in more than 70% of patients with asthma some antiepileptic drugs (AEDs) induced complete and stable remission ***(Lomia et al, 2004, 2005).***

BRONCHIAL ASTHMA

The word 'asthma' is derived from the Greek *aazein*, meaning "sharp breath". Asthma was first recognized and named by Hippocrates circa 450 BC. During the 1930s–50s, asthma was considered as being one of psychosomatic illnesses. Its etiology was considered to be psychological, with treatment often based on psychoanalysis and other 'talking cures' ***(Opolski and Wilson, 2005).***

Definitions

Asthma is a chronic disorder characterized by airway inflammation, reversible airway obstruction and airway hyperresponsiveness (AHR); in which eosinophils, mast cells and neutrophils play important roles in its pathogenesis ***(Kazuyuki and Makoto, 2011).***

Asthma is a chronic inflammatory disease of the airways characterized by infiltration and activation of inflammatory cells and by structural changes, including subepithelial fibrosis, smooth muscle cells hypertrophy/hyperplasia, epithelial cell metaplasia and angiogenesis ***(Ribatti et al., 2009).***