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Pathomechanisms of Viral Infections in the Respiratory Tract and Possibilities of Intervention

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Abstract

Viral pathogens responsible for infections of the respiratory tract, such as influenza, bird flu, swine flu, but also coronavirus are not primarily cytopathogenic. Virus-infected epithelial cells have to be eliminated by the body's own defence mechanisms e.g. macrophages, killer lymphocytes etc. This requires an increase of permeability of the capillary bed in which - mediated by proinflammatory cytokines (LOX, COX, PGE2, LTB4, Il2). An excessive production of these proinflammatory cytokines (cytokine storm) leads to an increased permeability of the capillary bed in many organs – resulting in multiorgan failure and death. Succesful therapy requires a mitigation of the overexpression of cytokines in the entire body. This can be achieved by corticosteroids with known side effects. However various herbal extracts (1.8. cineol, triterpenes) have been found to block the production of these proinflammatory cytokines effectively.

Introduction

Viral pathogens responsible for infections of the respiratory tract, such as influenza, bird flu, swine flu, but also coronavirus are not primarily cytopathogenic. This means that they don´t destroy the infected epithelial cell but reprogram the metabolism of infected epithelial cells so that the epithelial cells produce and excrete thousands of copies of the virus. If the viruses would destroy the cell, there would no copies. Some of these epithelial cells eventually die from exhaustion, the majority of these virus-infected epithelial cells have to be eliminated by the body's own defence mechanisms e.g. macrophages, killer lymphocytes etc.. This requires an increase of permeability of the capillary bed in which - mediated by proinflammatory cytokines (LOX, COX, PGE2, LTB4, Il2) - the capillary bed becomes more permeable so these effector cells can reach the infected epithelial cells from the blood stream. Proinflammatory cytokines are also responsible for the symptoms of a viral infection such as fever, fatigue, joint pain, etc.

In principle, this mechanism is useful because it has a favourable effect on the natural course of the virus infection and eliminates virus-infected epithelial cells. However, problems arise when an excessive release of these proinflammatory cytokines leads to an expansion of the capillary bed in many organs. The cytokine release syndrome (CRS) seems to affect patients with severe conditions. The general expansion of the capillary bed in various organs of the body such as the liver, spleen, kidney, heart results as a consequence in multi-organ failure. This phenomenon is known under the term "cytokine storm".

Blockage of proinflammatory cytokines by herbal extracts: The cytokine storm can be mitigated by the administration of corticosteroids; this however impairs of the bodys own defense mechanisms. It is now possible to reduce the precursors of these proinflammatory

cytokines, namely the arachidonic acid metabolism in the body, responsible for the formation of COX and LOX and to block the excessive formation of these proinflammatory cytokines.

Groundbreaking studies by Juergens have shown that 1.8 cineol but also triterpenes, which are found in many plant extracts, inhibit formation of prostaglandin E2, leukotriene B4, and interleukin1 almost to 100% (Figure 1) [1].

Eucalyptol, also known as 1,8-cineol, is a monoterpene and has been shown to exert anti-inflammatory and antioxidant effect. It is traditionally used to treat respiratory disorders due to its secretolytic properties. The effect of 1,8-cineol on pulmonary inflammation in a mouse model of acute lung injury has been evaluated. It has been demonstrated that 1,8-cineol significantly decreased the level of TNF-α and IL-1β, and increased the level of IL-10 in lung tissues after acute lung injury induced by lipopolysaccharide (LPS). It also reduced the expression of nuclear factor kappa B (NF-κB) p65 and toll-like receptor 4 (TLR4), and myeloperoxidase activity in lung tissues. In addition, 1,8-cineol reduced the amounts of inflammatory cells in bronchoalveolar lavage fluid (BALF), including neutrophils and macrophages, and significantly decreased the protein content in BALF and the lung wet/dry weight (W/D) ratio. Its effect on LPS-induced pulmonary inflammation was associated with suppression of TLR4 and NF-κB expressions. The results provide evidence that 1,8-cineol inhibits acute pulmonary inflammation, indicating its potential for the treatment of acute lung injury. Prostaglandin E2 is a lipid, arachidonic acid-derived prostaglandin hormone that is produced by the activity of cycloxygenase-2. Its functions include the regulation of inflammatory responses and vascular smooth muscle activity by acting on a family of GPCRs (EP1–EP4). Due to their antiinflammatory effect, plant extracts slow down the excessive action of proinflammatory cytokines, help to improve lung function and thus prevent multiorgan failure.

Figure 1 shows a nearly 100% inhibition of PGE2, LTB 4 and IL1 by triterpenes from herbal extracts after LPS stimulation of monocytes.

The inhibition of the formation of proinflammatory cytokines has been documented by blocking the arachidonic acid metabolismus by 1.8. Cineol but also by Triterpenes (e.g. in extracts of primulae) after LPS stimulation of Monocytes [2].

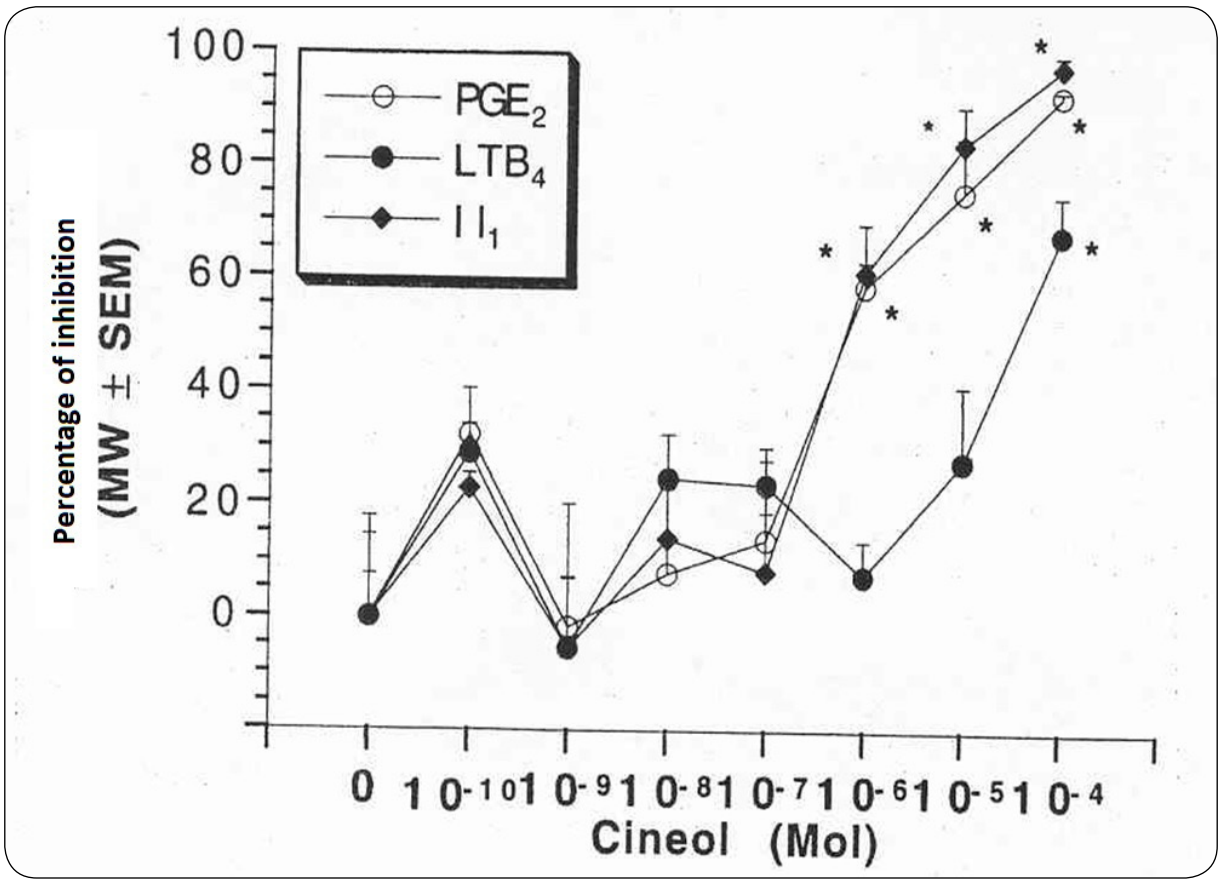

Figure 1: Inhibition of arachidonic acide metabolisms by triterpene (e.g. in extracts of primulae) after LPS stimulation of monocytes.

The anti-inflammatory effectiveness of cineol is comparable to that of corticosteroids without the side effects of corticosteroids on the body's own defence mechanisms against infections [3].

Figure 2 shows a 60-75% inhibition of LTB4 by blocking the arachidonic acid metabolismus by 1.8. cineol (i.e., in extract of primulae) after LPS stimulation of monocytes. 1.8. cineol is as effective as Corticosteroids.

There are also additional favourable properties as repair mechanisms i.e., scarring from intense inflammatory activity on lung tissue don't contribute to continued lung damage.

It is therefore prudent to use phytopharmaceutical products in the treatment of these respiratory infections. Other beneficial effects such as an improvement in the mucociliary clearance, an increase in the ciliary beat

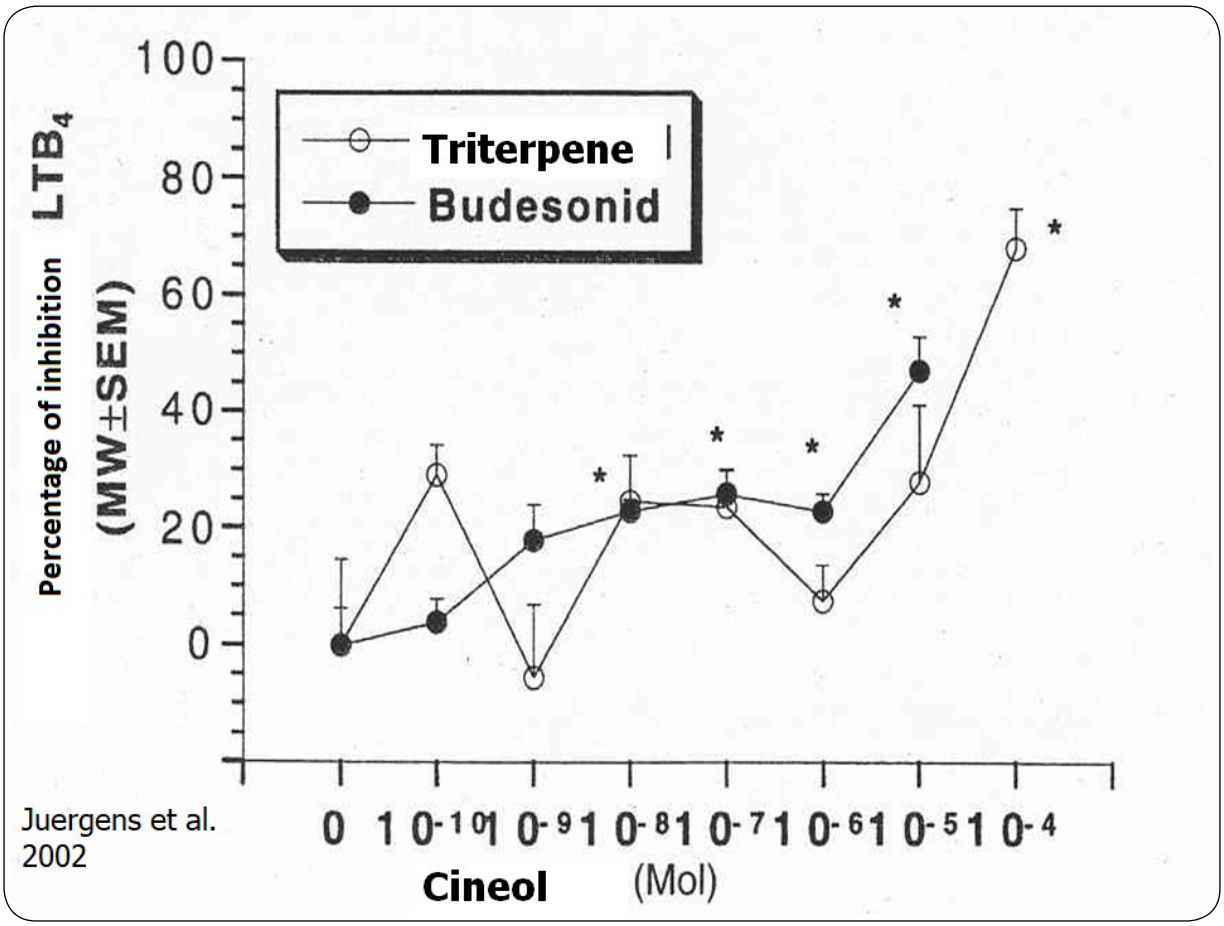

Figure 2: Inhibition of arachidonic acid metabolisms by 1.8. cineol (i.e. in extract of primulae) after LPS stimulation of monocytes.

frequency and liquefaction of the viscous secretion are also achieved [4].

Triterpenes (1,8 cineol) are contained in numerous plant extracts like thyme, ivy, primrose, gentian, but also in elderberry, lovage. Drugs available in Europe: Sinupret, Bronchipret, Bronchikum, Soledum. Triterpenes are also present in a number of herbal teas containing thyme, primulae, sorrel, elder flower and gentian.

P.S.: Phytopharmaceuticals as TCM have been an important remedy particularly in the treatment of patients infected with corona virus in China [5].

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