

OFFPRINT/TRANSLATION

HERBAL MEDICINE

Mechanism of action of ivy extract deciphered

→ An indirect β_2 -sympathomimetic effect on lung and bronchial cells explains the effect of ivy known from clinical studies in cases of respiratory catarrh and inflammatory and obstructive respiratory tract disease. Recent studies show that ivy saponins such as α -hederin inhibit the inactivation of β_2 receptors in the lungs and bronchi. As a result, tissue remains responsive for any adrenaline that is present. The epithelial cells of the lungs form more surfactant, which lowers mucus viscosity thus making it easier to cough up; the bronchial muscles relax.

Various theories can be found in the literature on the



The known efficacy of ivy extracts in case of inflammatory and obstructive airway diseases is due to an indirect β_2 -sympathomimetic effect on the cells of the lung epithelium and of the bronchi, resulting in an increase of secretolysis and bronchiolysis.

Photo: Prospan

secretolytic effect of saponaceous drugs such as ivy leaves or primula root: saponins are thought to irritate the mucous membrane of the stomach and, through reflex stimulation of afferent parasympathetic fibres, stimulate the goblet cells in the bronchial mucosa to produce more secretion. The spasmolytic properties of ivy extract are supposed to come from the parasympatholytic effects of certain glycosides. According to Prof. Hanns Häberlein from the University of Bonn, these two suppositions, which have never been demonstrated experimentally, have proved to be false.

 β_2 -adrenergic effects make ivy effective

According to Häberlein, the saponins hederacoside C and α -hederin found in the leaves are responsible in particular for the cough-relieving effect of ivy extracts. In addition to α -hederin, ivy leaves contain the precursor thereof, i.e. hederacoside C (which is converted into α -hederin by esterases) as well as its aglucone hederagenin. Using spectroscopic and immunohistochemical methods, the working group investigated the biochemical effects of these saponins, which, according to their findings, unfold via the G protein-linked β_2 -adrenergic receptors of the epithelial lung cells.

How the respiratory tract cell regulates the adrenaline signal

The cell membrane hosts the β_2 receptor among other highly organised functional units, which are able to move and which are therefore called lipid rafts. The intensity of the adrenaline effect on the cell is regulated in the lipid rafts, where the β_2 receptor is turned on and is relatively mobile. In the event of overstimulation, the activated β_2 adrenergic receptor is turned off: ligand receptor complexes are redistributed from the lipid rafts into the cell. These cell membrane intussusceptions (*coated pits*) are ligatured by the cell and finally absorbed in the form of small containers (early endosomes) into the inside of the cell. This process is called internalisation or endocytosis; the cell practically „swallows“ a number of its receptors in order to avoid superexcitation.

According to Häberlein's investigations, the main effect of ivy extract consists of the fact that α -hederin inhibits the endocytosis of β_2 receptors. The active saponin substance retains a large number of the activated β_2 receptors in the lipid rafts and prevents them from endocytosis. As a result, more functioning receptors are present on the surface of the cell. The adrenaline present can take more effect.

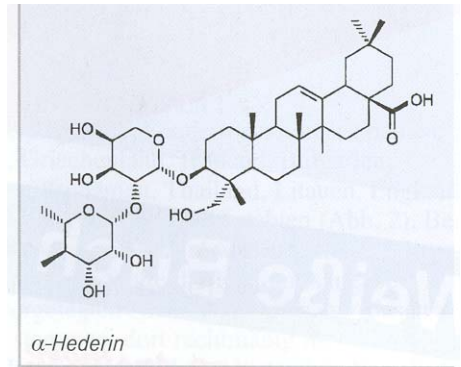
Ivy intensifies the adrenaline signal in the respiratory tract

The intensified β_2 adrenergic response of epithelial lung cells and bronchial muscles following the administration of ivy ultimately increases secretolysis and bronchospasmolysis:

As adrenaline activates adenylate cyclase, more cAMP (cyclic 3',5'-adenosine monophosphate) is formed from

Keyword: Surfactant

Surfactant is a mixture of substances which protect the alveoli from collapsing at the end of the expiration phase by lowering the surface tension of the liquid film on the alveoli. Surfactant optimises the ventilation of the lungs, facilitates oxygen and carbon dioxide exchange and improves the transport of mucus. For this purpose, surfactant is constantly produced in type II epithelial alveolar cells, packed into small containers (vesicular structures, called lamellar bodies) and released to the surface through exocytosis.



ATP (adenosine triphosphate). In addition to other various effects on metabolism, cAMP starts the formation of surfactant in the lung epithelium.

As do phosphatidylcholines, surfactant protein B in particular reduces surface tension, which, in turn, lowers the viscosity of viscous mucus, thereby making it easier to cough up according to Häberlein. This secretolytic activity can then exert soothing and cough-relieving effects on the bronchi.

Ivy loosens secretion and bronchoconstriction

In clinical studies, ivy extract also came up with bronchospasmolytic effects in addition to secretolysis. According to the investigations carried out by Häberlein's working group, this effect is also able to be explained by an intensified β_2 adrenergic response and increased cAMP production: a principle effect of increased cAMP production is the lowering of the intracellular Ca^{2+} concentration, as a result of which unstriated muscles, such as the bronchi, relax.

The group was able to demonstrate, by means of fluorescence correlation spectroscopy (FCS) and immunohistochemical methods, that α -hederin inhibits, depending on the concentration, the internalisation of β_2 adrenergic receptors at epithelial lung cells: a significant drop (50 to 80%) in the endocytosis of β_2 receptors through α -hederin was achieved ex vivo at concentrations between 0.5 μM and 1 μM , concentrations, which, in vivo, lie clearly below the toxic limit.

Put ...

... to Professor Dr. Hanns Häberlein, Institute of Physiological Chemistry, University of Bonn

? Is, according to your investigations, ivy extract also a remedy for asthma as well as for cough?

Häberlein: α -hederin in ivy extract increases the β_2 adrenergic response of epithelial lung cells and bronchial muscles. We are not dealing, however, with a β_2 -agonist here. Ivy is not, therefore, an anti-asthmatic in the true sense. For the stimulation of β_2 receptors through ivy extract is an indirect effect, which is dependent on the presence of direct agonists such as adrenaline or specific synthetic β_2 mimetics such as terbutalin, salbutamol and fenoterol, which are used as asthma relievers.

? Are there any therapeutic consequences?

Häberlein: As clinical studies have already shown, the bronchodilating effect of ivy extract practically corresponds with that of an inhalational β_2 sympathomimetic. According to our studies of the mechanism of effect, standardised dried ivy leaf extract is the obvious partner for these substances. This needs, however, to be confirmed by further studies.

References:

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Ralf Schlenger, Munich

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