A rat model for testing anti-inflammatory action in lung and the effect of glucocorticosteroids (GCS) in this model

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It has been observed in patient studies that a better differentiation between antiasthmatic action in the lung and inhibition of adrenal function is reached by inhaled GCS (e.g. budesonide BUD) than that attained by oral GCS [1]. The reasons for the better differentiation reached by inhaled GCS are not known. One proposed but still unproved reason is that inhaled GCS act by local (topical) activity on airway mucosa and lung microvasculature, before they are absorbed and 'diluted' in the systemic circulation. The aim of the present study was to create a GCS sensitive airway inflammation in a rat model and to study the importance of the route of GCS administration for the...
Budesonide is a focal bronchiolitis and alveolitis with an immediate reaction, but after some hours the beads attract inhibition of hypothalamus-pituitary-adrenal axis. The relationship between anti-inflammatory action in lung and inhibition of hypothalamus-pituitary-adrenal axis.

Bronchiolitis and alveolitis were induced in male SD rats (220 g) by intratracheal (i.t.) instillation of Sephadex beads (5 mg/kg). Sephadex consists of dextran to which rats have an endogenous hypersensitivity [2]. There is no immediate reaction, but after some hours the beads attract neutrophils, eosinophils and macrophages. These form cuffs around the beads, which are situated for the first hours in bronchioles and later on also more peripherally. The histological picture is a focal bronchiolitis and alveolitis leading to a peribronchial and interstitial edema and to impaired ventilation. These pathological changes can be quantified by the gain of lung wet weight, the rise in which correlates in time with the infiltration of granulocytes (esp. of eosinophils) and with the impaired ventilation. After one day the lung weight increases by 50–75%, the weight gain persisting for at least 4 days.

BUD given by i.t. instillation 30 min before Sephadex counteracted partly (dose 0.1 mg/kg) or nearly completely (dose 1 mg/kg) the wet lung weight gain, impaired respiratory changes, histological changes and influx of eosinophils [3]. To study if the protection induced by i.t. instillation depends on a local action, a refined model was used in which only the left lung lobe was pretreated with instilled BUD while Sephadex was given to both lung halves. The consistent result of such tests has been that the same protection against edema was obtained in the right as in the locally treated left lung lobe. This demonstrates that the anti-edema efficacy of i.t. instilled BUD does not rest on a local action at the application site in lung.

To be able to study adverse effects on adrenal function Sephadex-treated rats were given BUD twice a day for four days. At sacrifice the gain in wet lung weight and the adrenal weight were determined. Six routes of BUD administration were tested and the results are given in Fig. 1. When BUD was given by i.t. instillation, inhalation or i.v. injection, it was possible to inhibit the lung edema formation by up to 50% without reducing the adrenal weight. Such a differentiation between lung and adrenal effects was not attained with three other routes tested (Fig. 1). Diminished lung edema formation by 50% was then coupled to reduction of the adrenal weight by ~10% (after oral administration) or by ~20% (after epicutaneous or continuous from s.c. minipumps). Thus, the route of BUD application affected the relationship between lung and adrenal effects markedly but there was no simple correlation between selective lung action and the local mode of application to the lung.

The levels of circulating BUD in plasma were determined after 3 routes of administration: i.t. and i.v. representing routes differentiating between lung and adrenal effects and epicutaneous as a route without such separation. Doses with about the same anti-edema efficacy in lung were selected (i.t. and i.v. 0.3–0.4 mg/kg and epicutanously a dose about ten times higher). BUD was determined with a RIA method [4]. I.v. and i.t. administration gave rather similar plasma levels from 3 minutes onwards, but the i.v. values were higher for the first 2 minutes. After i.t. instillation the plasma levels of BUD were ~2000 nmol/l at 1 minute, ~40, after 3 h ~10 and after 6 h ~6 nmol/l. Epicutaneous administration gave no clear plasma peak, and the levels were stable at ~15 nmol/l between 1 and 6 hours. Figure 2 shows one experiment comparing the BUD levels in plasma after i.t. and epicutaneous application. At 1 h the epicutaneous levels were 3 times lower than the i.t. ones (p < 0.05), while at 6 h the opposite relation between the two application routes was noted.

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The plasma levels of BUD after i.t. instillation, 0.3 mg/kg, or epicutaneous application, 3 mg/kg. Mean ± s.e.m. of 5 rats.

The profile demonstrated by i.t. instilled or by inhaled BUD, marked anti-edema action in lung but low activity on adrenal weight, supports the relevance of the rat model, as inhaled BUD gives a principally similar differentiation in asthmatic patients. As studied in the rat model, the following proposals can be raised currently as reasons for lung selectivity reached by i.t. instillation:

1. it seems not to depend on a local action of BUD at the application site in lung;
2. analyses of BUD in plasma show that i.t. instillation leads to a very rapid systemic absorption of BUD. The plasma peak following i.t. administration is seen at ~1 minute, after which time the plasma levels drop rapidly. Epicutaneous administration leads to lower but more protracted BUD levels. It is suggested that these different types of plasma curves can explain why the former but not the latter administration route differentiates between lung and adrenal activity. If so, a rather short plasma peak of BUD is

![Figure 2](image-url)