INTRODUCTION

Drugs from a variety of pharmacological classes are known to adversely affect the respiratory system. Whole body plethysmography (WBP) is widely used in safety pharmacology to investigate in conscious animals the potential undesirable pharmacodynamic effects on respiratory function. The aim of this study is to show that WBP could also be used to study drug-induced changes in respiratory disorders that could be life-threatening or associated with significant morbidity, such as sleep apneas, cough or bronchospasm.

SLEEP APNEAS

**Animals**
- Male Sprague-Dawley Rat (350-390g)
- Standard housing conditions:
  - Room temperature 22 ± 2°C
  - Humidity 55 ± 10%
  - Lighting cycle: 12h:12h
  - Tap water and food (SAFE 44H & ad libitum)

**Experiments**
- **Day before experiment:** rats were placed in the plethysmograph chamber for at least 1 h-period for habituation to the experimental conditions.
- **Day of experiment:** after a stabilization period of at least 30 min, diapauses (2% isoflurane) or vehicle were administered orally (10 ml/kg).
- Sleep apneas were recorded for 5 hours, from 30 minutes post administration (required time for rats to fall asleep). Apneas parameters (total number, total duration and frequency) were therefore determined between 0-30 and 30-60, 60-90, 90-120, 120-150, and 150-180 min.
- Only sleep apneas with a duration of more than 3 s were retained for analysis and classified as follows:
  - <3 s: duration ≥ 3 s.
  - >3 s: duration ≥ 6 s.
  - >4 s: duration ≥ 10 s.

![Graph showing number of apneas over the 5-hour period for each drug (μg/kg)](image)

**CONCLUSION**

Experiments -30

COUGH

**Animals**
- Male Duster-Hardy Germes Pig (250-580g)
- Standard housing conditions:
  - Room temperature 22 ± 2°C
  - Humidity 55 ± 10%
  - Lighting cycle: 12h:12h
  - Tap water and food (SAFE 16H & ad libitum)

**Experiments**
- **Day before experiment:** animals were placed in a plethysmograph chamber.
- The cough was induced by inhalation of an aerosol of a 4 M citric acid solution.
- Citric acid was administered for 5 min with an ultrasonic nebulizer connected to the air-flow port of whole-body plethysmography boxes.
- The number of coughs over the last 10 min of nebulization was counted by a trained experimenter, based on characteristic animal posture, sound produced and respiratory signal.
- Baclofen (0.1-0.3 mg/kg, s.c.), codeine (100mg/kg, p.o.) or vehicle were administered 30 min before starting citric acid nebulization

![Graph showing number of coughs induced by citric acid nebulization](image)

BRONCHOSPASM

**Animals**
- Male Duster-Hardy Germes Pig (250-580g)
- Standard housing conditions:
  - Room temperature 22 ± 2°C
  - Humidity 55 ± 10%
  - Lighting cycle: 12h:12h
  - Tap water and food (SAFE 16H & ad libitum)

**Experiments**
- Guinea pigs were administered 3 weeks before experiment with 0.5 ml of saline containing ovalbumin (20 µg/ml) or 0.5 ml of ovalbumin hydrolysate (200 µg/ml).
- A nebulizer (20 mm) filled with water was introduced into the animal's respiratory tract. Cougher was scored independently and evaluated at the interquartile area. Experiments were performed in conscious animals the day after the challenge.
- All animals were pre-treated with propylthiouracil (1 mg/kg, i.p.) 30 min before the challenge.
- In sensitized animals, increasing doses of ovalbumin (1-3-10-30-60 µg/kg, i.v.) were injected at 10-minute intervals.
- In non-sensitized animals, increasing increasing doses of histamine (10-30-60-100 µg/kg, i.v.) were injected at 10-minute intervals. Mepyramine (10 mg/kg, i.v.) was administered 30 min before the challenge with histamine.
- Anesthetic enhanced pause (Perfus) was calculated by means of HEM software (Nonin) according to the following formula: Perfus = (The Derived R) x (P/F-R/P) x (R/T) x (P/F-R/P), where R/T: relaxation time evaluated at the time to achieve 64% of the total volume.

![Graph showing enhanced pause (Perfus) with histamine](image)

**REFERENCES**

These results show that whole body plethysmography is appropriate to evaluate the effects of new chemical entities on respiratory disorders such as sleep apneas, cough and bronchospasm.