Clara cell protein (CC16) as a biomarker for ozone exposure in humans

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AIRNET
A Thematic Network on Air Pollution and Health

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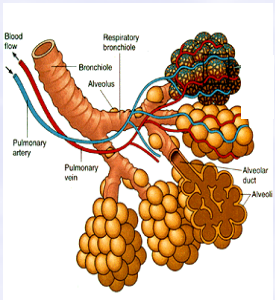
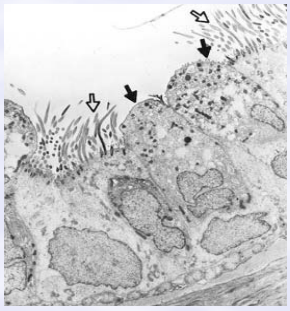
Background

Ozone (O_3) is an important air pollutant known to impair lung function and induce airway inflammation. Epidemiological studies have shown associations between variation in daily ambient levels of ozone and adverse health effects. Clara cell protein (CC16) is a 16-kDalton anti-inflammatory protein produced and secreted by the bronchiolar Clara cells. CC16 diffuses from the respiratory tract into the blood and has been considered a sensitive marker of increased permeability of the lung epithelial barrier (1). An association between serum CC16 and ambient ozone levels has been found in Italian cyclists and CC16 has been suggested to be a promising biomarker for ozone exposure (2).





Clara cell protein (CC16) is the major protein secreted by the bronchiolar Clara cells

Aim

To evaluate the usefulness of CC16 as a biomarker for ozone exposure by addressing its sensitivity under controlled experimental conditions.

Methods

Twenty-two healthy subjects were exposed to 0.2 ppm of ozone and filtered air on two separate occasions, at least three weeks apart. Peripheral blood samples were drawn and lung function assessed at five time-points: 2 hours pre-exposure, immediately before and after exposure as well as 2 and 4 hours post-exposure. CC16 was determined in serum using a latex immunoassay (3).

Results

Exposure to ozone significantly increased the serum concentrations of CC16 at two and four hours post-exposure relative to parallel air exposure values, 12.0±4.5 vs. 8.4±3.1 μg/L [mean±SD] ($p<0.001$) and 11.7±5.0 vs. 7.9±2.6 μg/L ($p<0.001$). Ozone serum CC16 concentrations at 2 h post-exposure were significantly increased compared to the immediate pre-exposure value ($p<0.01$). After air challenge, serum CC16 concentrations were significantly decreased at 2 and 4 hours post-exposure compared with the pre-air exposure concentration, $p<0.01$ and $p<0.001$ respectively. (Figure 1)

Plasma from archived material revealed that ozone exposure resulted in an increase in CC16 concentrations which persisted until 6 hours post-exposure; 9.1±2.6 vs. 7.1±1.7 μg/L ($p<0.01$) but returned to control values at 18 h post-exposure. (Figure 2)

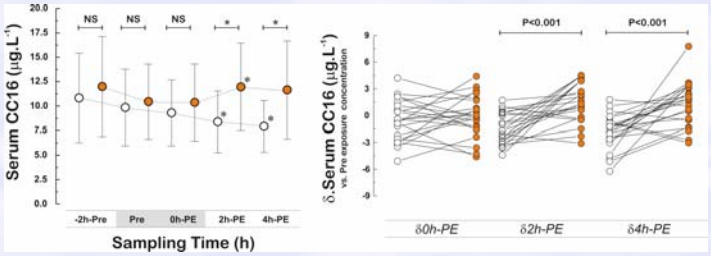


Figure 1

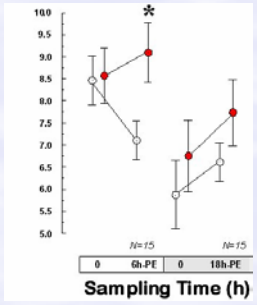


Figure 2

Ozone induced a significant decrease in FEV_1 immediately post exposure ($p=0.002$) (Figure 3). A corresponding fall was also detected in VC ($p=0.001$).

No significant correlations were observed between baseline serum CC16 concentrations and baseline lung function values. Neither was any relationship noted between the CC16 and lung function responses (ozone – air) at any time-point post-exposure.

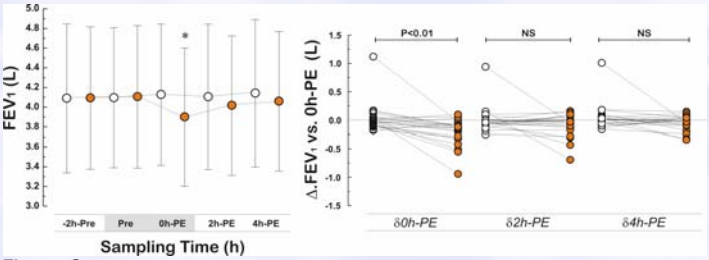


Figure 3

Discussion and Conclusions

Serum levels of CC16 increased after exposure to ozone, peaking around 2-4 hours post-exposure with levels back to baseline at 18 h.

As CC16 is synthesized and secreted almost exclusively by the lung Clara cells, the enhanced serum concentrations can only be explained by a leakage of the protein across the lung epithelial barrier.

Increases in serum CC16 seem to correspond with an evolving ozone-induced airway inflammation.

No association was observed between the magnitude of the ozone-induced lung function decrements and CC16 responses, suggesting that impaired lung function was not related to epithelial injury.

A consecutive decrease in CC16 levels was detected on the air exposure day. This may suggest a diurnal variation of the baseline CC16 levels.

The data suggest serum CC16 to have a potential as a biomarker for ozone exposure.

The question of a potential diurnal variation in baseline serum CC16 concentrations needs further evaluation.

References:

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2. Broeckaert *et al. Lancet* 1999;353:900-901
3. Bernard *et al. Eur Respir J* 1992;5:1231-1238

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