

# European Respiratory Society Annual Congress 2013

**Abstract Number:** 3531

**Publication Number:** P2146

**Abstract Group:** 1.1. Clinical Problems

**Keyword 1:** COPD - mechanism **Keyword 2:** Physiology **Keyword 3:** COPD - management

**Title:** Antagonism of substance P and perception of dyspnea in patients with COPD

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**Body:** Background: The objective of this study was to investigate whether substance P, an excitatory neuropeptide, modulates the perception of dyspnea by administering aprepitant, a selective antagonist that blocks NK-1 receptor signaling. Methods: Sixteen patients (age,  $70 \pm 6$  years) with COPD completed the study. At intervention visits, aprepitant (125 mg) or placebo was administered orally, and patients rated breathlessness during resistive load breathing (RLB). Blood levels of substance P and beta ( $\beta$ )-endorphin were measured. Results: After aprepitant, but not with placebo, there were significant increases in substance P ( $+54 \pm 39$  %) and  $\beta$ -endorphin ( $+27 \pm 17$  %); changes were significantly correlated (Spearman  $r = 0.62$ ;  $p = 0.01$ ). There were no differences in ratings of breathlessness during RLB between interventions.

Conclusions: Our results do not support a role for the substance P-NK-1 pathway in the perception of dyspnea in patients with COPD. These findings may be explained by opposing effects of excitatory (substance P) and inhibitory ( $\beta$ -endorphin) neuropeptides, released after administration of aprepitant, that affect perception.