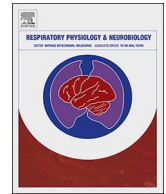




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Sensitivity of airway cough-related afferents is influenced by female sex hormones

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ABSTRACT

Chronic hypersensitivity cough syndrome affects mainly postmenopausal women; however, the pathogenesis of cough hypersensitivity in this demographic is not entirely understood. The role of sex hormones in cough has never been studied in detail; however, sex hormones seem to play an important role in the lung health of women. Our study was aimed to analyse the effect of female sex hormones (oestrogen – E2 and progesterone – Pg) on cough sensitivity measured by inhalation of capsaicin in follicular and luteal phases of menstrual cycle, characterized by significantly different concentrations of sex hormones. These data were compared with a matched group of women taking oral contraceptives. Cough sensitivity to capsaicin increased in luteal phase in subjects with normal menstrual cycle, and this functional change was not present in group with contraceptive pills. The cough sensitivity correlates with the Pg/E2 ratio, and relative lack of oestrogen in luteal phase is associated with higher cough sensitivity to capsaicin.

1. Introduction

Sex hormones seem to play an important role in the lung health of women and many effects of sex steroids on lung structure and function have been recognized so far (Sathish and Prakash, 2016). Decline of lung functions, increase of respiratory symptoms and asthma are associated with menopausal transition considering hormonal and metabolic factors (Real et al., 2008). Less, if none attention is angled towards hypersensitive cough syndrome, which affects mainly postmenopausal women. A high proportion of women visiting specialized cough clinics worldwide (Song et al., 2014) and studies demonstrating higher sensitivity of cough related airway afferents in women are an evidence of gender dimorphism (Dicpinigaitis and Rauf, 1998; Fujimura et al., 1996; Kastelik et al., 2002). It is suggested that female preponderance to exaggerated cough reflex has developed as an evolutionary mechanism to protect the airways against aspiration of refluxate during pregnancies, when reflux episodes are more frequent (Brooks, 2011; Ramya et al., 2014). It can also be a consequence of increased visceral sensitivity in women due to evolutionary selection pressure (Kvachadze et al., 2015). Differences in cough reflex are believed to be of hormonal

origin. They appear in the puberty after the rise of sex hormones (Varechova et al., 2008). Accumulating epidemiological and clinical data highlight the importance of sex hormones; however, these studies do not provide an explanation why exaggerated cough manifests in women mainly after the hormonal withdrawal (Morice, 2013; Song et al., 2014).

TRPV1 expressing vagal fibres play an important role in the cough reflex (Canning, 2006). TRPV1 is an ion channel responsible for activation of cough-related afferents in human airways (Morice et al., 2011). It is generally known that women are predominantly affected by functional disorders involving ion channels, and the influence of sex hormones on ion channels has long been recognized in human physiology (Patberg, 2011). Sex hormones also influence TRPV1 activation/sensitization, modulating the channel excitability. It was documented that activation of TRPV1 channel on pelvic nerves depends on the oestrous cycle (Peng et al., 2008). Also, more than 75% of the C fibres expressing TRPV1 co-express also oestrogen receptor α , suggesting a role of the oestrogen in regulating these cells. No data are available about the effect of sex hormones on airway afferents, sensitivity of which can be measured by quite simple methodology –

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capsaicin inhalation test (Morice et al., 2007). We aimed our study to determine the effect of female sex hormones on cough reflex sensitivity measured by capsaicin single-breath test in healthy women with normal menstrual cycle (MC) and women taking oral contraceptives (OC).

2. Methods

2.1. Ethical approval

The study was approved by the Committee for Ethics of the Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava under approval No. EK154/2014. Informed consent was obtained from all subjects involved in the study; however, subjects' information had been limited to the extent it did not interfere with the study purposes, as it is known that cough response could be modulated consciously.

2.2. Study population

The study population consisted of women, mean age 23 years, non-smokers, non-atopic, with normal lung functions tests, anterior rhinoscopy, and without acute respiratory infection in 4 weeks prior to measurements for each group ($n = 22$) (Table 1). Based on structured interviewer-led questionnaire, each subject was asked about respiratory symptoms, individual and family history of bronchial asthma, allergic rhinitis, gastroesophageal reflux, cardiovascular diseases and ACE inhibitor treatment.

The women were also examined by gynaecology specialists, to exclude all subjects with menstrual cycle irregularities and hormonal disturbances, which was confirmed by the tracking of hormonal profile and pelvic ultrasound for MC group. The subjects of OC group were selected based on the similar inclusion criteria, and they were taking monophasic hormonal contraception containing ethinyl-estradiol and dienogest with 21/7 pattern of use.

2.3. Assessment of cough sensitivity and urge-to-cough

Cough sensitivity testing was performed according to ERS guidelines (Morice et al., 2007) by inhalation of gradually increasing concentrations of capsaicin ranging 0.49–1000 μM all freshly made the day of testing. Each subject tested had taken lung function tests and inhalation of saline aerosol before increasing concentrations of aerosols of capsaicin solutions were administered.

Aerosols were produced by computer assisted compressed air driven nebulizer KoKo[®] Digi-Doser-Spirometer (nSpire Health Inc., Louisville, USA) with controlled nebulizer output per breath. The lowest concentration of capsaicin which induced two or more coughs (C2) and five or more coughs (C5) were determined; according to the ERS guidelines, only coughs that appeared immediately after aerosol inhalation had been counted.

Urge-to-cough is defined as the sensation of airway irritation that precedes the motor act of coughing; this phenomenon represents cortical contribution to the airway defence (Davenport, 2007). We used the method described by Dicipinigaitis et al. (Dicipinigaitis et al., 2011), we asked our subjects to evaluate and describe verbally the feelings regarding the urge-to-cough after each capsaicin inhalation within the range 0–10 (0 – no urge at all; 10 – urgent need for cough).

Table 1
Characterization of study population.

	Age	Height (cm)	Weight (kg)	BMI	FEV1/FVC
MC group	23.7 \pm 1.3	170 \pm 1.3	66.7 \pm 2.9	21.6 \pm 0.6	103 \pm 0.09%
OC group	22.4 \pm 0.4	166 \pm 2.0	55.1 \pm 2.8	20.4 \pm 0.9	107 \pm 0.07%

Data are presented as mean \pm SEM (standard error of mean).

Concentration at which the urge-to-cough had occurred was registered.

2.4. Measurement of exhaled nitric oxide

Exhaled nitric oxide (FeNO) was measured by analyzer NIOX MINO[®] (Aerocrine, Solna, Sweden). FeNO was determined during single-breath exhalation against a constant, positive counter-pressure of 10–20 cmH_2O to ensure an exhalation flow rate of 50 ± 5 ml/s, in accordance with the ATS/ERS guidelines (“ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005,” 2005). FeNO concentration is expressed in ppb (parts per billion).

2.5. Data analysis

Capsaicin cough thresholds C2, C5 and urge-to-cough are expressed as geometric mean with 95% confidence interval. FeNO and lung function tests are expressed as mean and standard error of mean. For the statistical analysis, repeated measures ANOVA and Friedman's test as appropriate were employed using statistical programme GraphPad InStat. The differences were considered significant at $P < 0.05$. Correlation coefficients were calculated using Spearman correlation analysis in aforementioned software.

2.6. Study protocol

Subjects were assessed twice during the menstrual cycle. First assessment of all parameters was performed in the follicular phase of the cycle between the day 3–5 and the second assessment was performed during the luteal phase between the days 21–23. Blood samples, pelvic ultrasonography and all cough-related measurements were performed likewise. The days of measurements were selected by an expert in gynaecological endocrinology.

3. Results

3.1. Hormonal values

Measurements of hormonal values in follicular phase and luteal phase of menstrual cycle (Table 2) indicate that our subjects had physiological values of sex hormones with statistically significant differences in oestrogen, progesterone and FSH (follicle stimulating hormone) levels, as expected. The data are in agreement with a general concept of a physiological menstrual cycle, cyclic fluctuation of sex hormones values and their ratios during the menstrual cycle.

3.2. Cough sensitivity and urge-to-cough

Cough sensitivity expressed as C2 and C5 increased (therefore the threshold decreased) significantly in luteal phase from 91.2 (89.45–92.95) μM to 58.7 (57.11–60.29) μM (geometric mean with 95% CI, $P = 0.0313$) for C2 and 364.9 (363–366.8) 250.0 (247.88–252.12) μM (geometric mean with 95% CI, $P > 0.05$) for C5.

Data obtained for subjects in contraceptive group did not show significant differences between the first and the second measurement during the cycle neither for the C2 (143.6 (141.4–145.8) μM vs. 189.5 (186.99–192.01) μM) nor C5 values (250 (247.39–252.61) μM vs. 435.3

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