Ketanserin attenuates cigarette-mediated oxidative stress in human bronchial epithelial cells

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Introduction: Chronic obstructive pulmonary disease (COPD) is characterised by progressive airway limitation. Although the pathology of COPD is not fully understood, disruption of the oxidant-antioxidant homeostasis has been suggested to stimulate inflammatory reactions in the lung (Crapo, 2003). Cigarette smoke (CS), one of the major causes of COPD, is abundant in reactive oxygen species (ROS) that can induce oxidative stress. Ketanserin, a selective serotonin receptor 2 (5-HTR_2) antagonist, has been reported to improve lung function in COPD patients (Cazzola et al, 1990) through unknown mechanisms. On the other hand, activation of 5-HTR_2 has been suggested to generate ROS in rat renal mesangial cells (Greene et al, 2000). We therefore hypothesise that 5-HTR_2 is involved in CS-mediated oxidative stress, leading to inflammatory responses in the lungs. The present study aimed at investigating whether ketanserin protects bronchial epithelial cells from CS-induced oxidative stress and inflammatory responses.

Methods: The human bronchial epithelial cell line (BEAS-2B) was cultured to 80% confluence in complete keratinocyte-SFM before treatment. Release of a pro-inflammatory marker, IL-8, was determined by ELISA. Oxidative stress was assessed by the ratio of reduced glutathione (GSH) to glutathione disulfide (GSSG) using spectrophotometric assay.

Results: Our results demonstrated that CS significantly increased the IL-8 level (23.1±4.5 vs 8.5±0.9 pg/mL for CS-exposed and control cells respectively; $P<0.01$) and decreased the GSH/GSSG ratio (21.2±4.6 vs 43.9±10.5; $P<0.001$). Ketanserin (10 nM) completely reversed CS-induced IL-8 elevation and significantly restored CS-induced oxidative stress.

Conclusion: These data indicate the possibility that ketanserin may be beneficial in restoring CS-mediated oxidative stress and hence inflammatory responses.

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Triiodothyronine promotes cardiac differentiation of embryonic stem cells through PI3K-Akt pathway

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Introduction: Thyroid hormones (3,5,3′-triiodothyronine [T_3]) play a crucial role in cardiac physiology and are implicated in the development of cardiac hypertrophy. Thyroid gland and heart have close temporal and spatial relationship during embryonic development. The effects of T_3 through cardiac foetal gene programming on adult cardiomyocytes have been well characterised; however, it is unclear whether T_3 exerts any effects on cardiac differentiation of embryonic stem cells (ESCs).

Methods: Murine embryonic stem cell (mESC), D3, was used for cardiac differentiation in the current study. Troponin-T positive cells were counted as the ESC-derived cardiomyocytes (ESC-CM) by FACS. RT-PCR analysis revealed the mRNA expression of cardiac specific markers and calcium handling proteins. Furthermore, the calcium handling properties of ESC-CMs were examined by fluorescence confocal microscopy. The underlying mechanism of cardiac differentiation mediated by PI3-Akt pathway was studied by western blotting.

Results: T_3 promotes cardiac differentiation of ESCs as evidenced by an increase in the number of troponin-T positive cells counts. Consistently, mRNA levels of early and late cardiac markers including NK2 transcription factor–related locus 5 (Nkx 2.5), myosin light chain 2 ventricular transcripts (MLC2V), alpha- and beta-myosin heavy chain (A and B-MHC) are also increased with T_3 treatment. Functionally, ESC-CMs treated with T_3 appear to have a more mature calcium handling phenotype with a significant increase in the maximum upstroke velocity, which agreed with the up-regulated ryanodine receptor-2 (RyR2) level. Furthermore, inhibition of PI3/Akt signalling by LY294002 hence suggesting T_3 induces cardiac differentiation and maturation via the Akt pathway.