European Respiratory Society
Annual Congress 2013

Abstract Number: 1356

Publication Number: P4258

Abstract Group: 6.3. Tobacco, Smoking Control and Health Education

Keyword 1: Lung growth/development **Keyword 2:** Smoking **Keyword 3:** No keyword

Title: Role of oxidants during lung development and bronchial hyper-reactivity after in utero nicotine exposure

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Body: Maternal smoke during pregnancy is associated with several adverse fetal outcomes that strongly increase the susceptibility to develop secondary diseases in late infancy. Nicotine, the principal active component in cigarette smoke, can freely cross the placenta and accumulate in the developing fetus and in maternal milk, affecting lung development and reducing pulmonary functions. In vitro, nicotine can directly increase reactive oxygen species (ROS) production in different cell types, suggesting their possible involvement in nicotine-induced oxidative stress. In this study we aim to characterize the NADPH oxidase (NOX) contribution to nicotine-mediated oxidative stress. We therefore cultured MLE-12, a lung epithelial cell line, with saline or-with 1μM or 100μM nicotine for 48 hours. Nicotine increased ROS production as well as apoptosis, as assessed by dihydroethidium staining, TUNEL staining and cleaved caspase-3 levels. ROS production was blocked in a stably transfected MLE-12 with NOX1 shRNA. We also exposed pregnant wild-type mice to oral saccharin (2%, control) or nicotine (200 ng/ml in 2% saccharin) during the gestation and for 16 days after birth. Pups were euthanized at day 2, 8 and 16 (postnatal, PND); we observed a significant increase in the expression of NOX1, NOX2 and NOX4 mRNA in lungs of PND2 pups. These preliminary results suggest that nicotine can induce oxidative stress, counteracted by genetic ablation of NOX1, and caspase-mediated apoptosis in a murine lung epithelial cell line and a possible involvement of NOXs enzymes in nicotine-induced lung development alterations in utero.