Karolinska Institutet

Institutionen för Fysiologi och Farmakologi

Nitric Oxide in Experimental Pulmonary Embolism

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Samuelssonsalen, Tomtebodavägen 6

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ABSTRACT

Nitric oxide (NO) is an important modulator of the pulmonary circulation both at basal state and in pulmonary hypertension. Low levels of NO are detectable in exhaled gas which is believed to mirror pulmonary NO formation and elimination. Pulmonary embolism is a disease characterised by pulmonary hypertension, and thereby increased afterload of the right ventricle, and by disturbed gas exchange which produces hypoxemia. The role of NO in acute pulmonary embolism was studied in two animal models.

The fraction of NO in exhaled gas increased dramatically after induction of acute pulmonary embolisation with both gas and solid emboli. It was found that approximately 50% of the increased exhaled NO could be reversed by normalising the airway/alveolar carbon dioxide concentration, thus indicating a regulatory role of carbon dioxide on pulmonary NO production in this condition.

Endogenous NO production exerts a protective effect in acute pulmonary embolism since it was found that inhibition of endogenous NO production in combination with pulmonary embolisation resulted in a severely augmented hemodynamic response and significantly impaired the survival in this condition. Therefore it was further hypothesised that exogenous NO might be protective in this condition.

NO donor compounds, some of which were novel organic nitrites, with increased selectivity towards the pulmonary circulation were developed. Intravenously administered organic nitrites reduced the pulmonary hypertension and relieved the strain on the right ventricle in acute pulmonary embolism without adverse effects in the form of systemic hypotension, methaemoglobin formation and tolerance development. Methods for identification and characterisation of organic nitrites were described, including a novel HPLC-NO/nitrite analysis.

These studies show that exhaled NO is increased after acute pulmonary embolism thus emerging as a potential diagnostic aid in this condition. Endogenous NO is protective in acute pulmonary embolism which provides further knowledge on the role of NO in the pulmonary circulation. Exogenous NO, in the form of certain organic nitrites, exerts beneficial effects in acute pulmonary embolism, thus rendering organic nitrites as a potential future life-saving treatment in acute pulmonary embolism. Future studies will investigate the effects of organic nitrites in experimental models of other life-threatening diseases with compromised pulmonary circulation.

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