The serotonin pathway – a therapeutic target for pulmonary hypertension? Assessing vascular function using synchrotron radiation microangiography

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Blockade of the serotonin reuptake transporter (5-HTT), using fluoxetine, has been identified as a potential therapeutic target for preventing and, importantly, reversing pulmonary hypertension (PH). This study utilized synchrotron radiation (SR) microangiography to determine whether fluoxetine could prevent or reverse endothelial dysfunction and vessel rarefaction, which underpin the disease PH.

Following one injection of monocrotaline (MCT, 60 $mg \cdot kg^{-1}$), rats received daily injections of either saline or fluoxetine (MCT+Fluox, 10 $mg \cdot kg^{-1}$) for three weeks. A third group of rats also received the fluoxetine regime, but only three weeks after MCT (MCT+$Fluox_{Delay}$). Control rats received daily injections of saline. Pulmonary microangiography was performed to assess vessel branching density and visualize dynamic changes in vessel diameter following; i) acute fluoxetine, or ii) acetylcholine, sodium nitroprusside, BQ-123 ($ET\text{-}1_A$ receptor blocker) and L-NAME (NOS inhibitor).

Monocrotaline induced PH in a rat that was inevitably terminal. Delayed treatment of fluoxetine (MCT+$Fluox_{Delay}$) was unable to reverse the progression of PH. Moreover, early fluoxetine treatment pre-PH (*i.e.* MCT+Fluox) did not prevent pulmonary endothelial dysfunction, vascular remodeling, vessel rarefaction and an increase in pulmonary pressure, so that MCT+Fluox rats were no different to untreated MCT-rats. Interestingly, fluoxetine treatment did, counter-intuitively, prevent the onset of right ventricular hypertrophy.

Using synchrotron radiation microangiography, we conclusively demonstrated that selective blockade of the serotonin reuptake transporter alone is not sufficient to prevent pulmonary endothelial dysfunction or the inevitable decline of vessel rarefaction. Accordingly, potential therapeutic strategies should aim to target multiple pathways to ensure an optimal outcome.