The effects of gender on the development of dexfenfluramine-induced pulmonary arterial hypertension in mice

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The ‘serotonin hypothesis of pulmonary arterial hypertension’ (PAH) arose after an outbreak of the disease was reported amongst women taking the anorexigenic drugs aminorex and dexfenfluramine, both of which are serotonin transporter substrates. Recently, we have shown that female mice deficient in tryptophan hydroxylase 1 (the rate limiting enzyme in the synthesis of serotonin) are protected against dexfenfluramine-induced PAH, providing evidence that dexfenfluramine mediates PAH in mice via its effects on the serotonin system. As idiopathic and familial PAH occurs more commonly in women than in men (>2:1), we wished to investigate the effects of gender on the development of dexfenfluramine-induced PAH in mice.

Male and female mice (C57/BL6xCBA, 15-30g, 2-3 months old) were dosed with dexfenfluramine (5mg.kg\(^{-1}\)day\(^{-1}\) PO for 28 days) or vehicle control. Mice were then anaesthetised using isoflurane and right ventricular pressure (RVP) obtained via a needle inserted directly into the right ventricle. Pulmonary vascular remodelling was assessed by calculating the percentage of remodelled pulmonary arteries <80µm i.d. Statistical analysis was by two-way analysis of variance. Data are expressed as mean±s.e.m.

Dexfenfluramine increased systolic RVP (sRVP; 32.25±0.46mmHg cf 19.24±2.03mmHg, p<0.001) in female mice, but not in males (21.78±2.62mmHg cf 23.66±0.51mmHg, p>0.05). Dexfenfluramine also increased pulmonary vascular remodelling in female mice (12.10±1.17% cf 3.22±0.32%, p<0.001) but not in males (3.01±0.88% cf 3.36±0.40%, p>0.05).

In conclusion, female gender is permissive in the development of PAH resulting from dexfenfluramine ingestion in mice. As the effects of dexfenfluramine on the development of PAH are thought to be mediated via the serotonin system, these results suggest that interactions between the serotonin system and female gender predispose to the development of PAH in mice.