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Title: Effect of fulvestrant in an experimental model of hepato-pulmonary syndrome (HPS) in rats

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Body: It has been postulated that general vasodilatation, and in particular in the lung, observed in portal hypertension is explained in part by an increased level of estradiol most likely through an enhanced endothelial formation of nitric oxide (NO). The present study has investigated the possibility that blockade of the estrogen receptor by fulvestrant (F) is able to decrease the NO formation and thus might improve the HPS. HPS was elicited by chronic bile duct ligation (CBDL). Rats were divided into four groups : CBDL, CBDL+F, sham (S) and S+F. Plasma nitrites and nitrates concentrations were higher in CBDL group compared to the S group; this effect was not affected by F. In the lung, the endothelial nitric oxide synthase (eNOS), and nitrotyrosine protein expressions were increased in CBDL group as compared to the S group, and this effect was significantly reduced by F. Surprisingly the level of pVASP (an indirect marker of NO formation) was decreased in the lungs of the CBDL group, and this effect was not affected by F. In contrast, the immunohistochemical level of vascular endothelial growth factor (VEGF) was increased in the lungs of the CBDL group, and it was unaffected by F. Thus, the present findings suggest that in the lungs of CBDL rats the excessive formation of NO may be degraded by superoxide anions leading to peroxinitrites and a decreased activation of the cGMP pathway, and that this effect is not affected by F. In addition, they further suggest that vascular remodelling may be promoted in the lungs in the HPS subsequent to the increased expression of VEGF and that this effect was not affected by F.