Phosphodiesterase 5 inhibitor attenuates pulmonary and right ventricular remodeling through an anti-proliferative mechanism

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Pulmonary arterial hypertension

• It is a major issue in cardiovascular medicine;

• It is associated with right ventricular (RV) hypertrophy, considered to be the result of RV pressure overload, and eventually RV failure;

• Chronic hypoxia (CH) can induce this disease;

• At present, little is known about mechanisms driving these responses.
Treatment

Phosphodiesterase type 5 (Sildenafil):

- Approved in standard protocols of PAH therapy
- Blocks breakdown of cGMP
Aim

We investigated the effect of phosphodiesterase-5 inhibition on pulmonary and right ventricular remodeling.
New system of hypoxic chambers (CHUV, Lausanne)

Animals remain continuously exposed to specific level of hypoxia

Experimental protocol

Adult male Dawley rats were divided in:

Group 1: **normoxia** 21% $O_2$, IP saline injections (n=12)

Group 2: **chronic hypoxia** (CH 10% $O_2$), IP daily saline injections (n=10)

Group 3: **CH+Sildenafil** 10% $O_2$, IP daily Sildenafil injections (Sild) (1.4 mg/Kg, n=12)
# Physiological parameters

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Chronic hypoxia (CH)</th>
<th>CH+ sildenafil</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight gain, g</strong></td>
<td>103±5</td>
<td>13±8*</td>
<td>3±5*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>PaO2, mmHg</strong></td>
<td>83.5±7.8</td>
<td>40.3±2.8*</td>
<td>42.5±2.8*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>PaCO2, mmHg</strong></td>
<td>39.3±2.0</td>
<td>26.1±2.5*</td>
<td>25.4±1.3*</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.43±0.01</td>
<td>7.40±0.02</td>
<td>7.42±0.02</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Base excess, mEq/L</strong></td>
<td>0.7±0.8</td>
<td>-8.3±0.8*</td>
<td>-8.2±0.5*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>cGMP, pmol/ml</strong></td>
<td>2.18±0.32</td>
<td>2.34±0.27</td>
<td>4.64±0.91*#</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Haematocrit, %</strong></td>
<td>41±2</td>
<td>66±1*</td>
<td>62±1*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Data are presented as mean± SEM; * p<0.05 vs Normoxia; # p<0.05 vs CH*
Cardiopulmonary function

Right ventricle M-mode

Normoxia  CH  CH+Sild

Pulse-wave Doppler across the pulmonary artery

RV wall thickness at diastole

P data are presented as mean± SEM; * p<0.05 vs Normoxia; # p<0.05 vs CH
Pulmonary and RV remodeling

Data are presented as mean± SEM; * p<0.05 vs Normoxia; # p<0.05 vs CH
In vivo BrdU incorporation in RV

Data are presented as mean± SEM; * p<0.05 vs Normoxia; # p<0.05 vs CH
Collagen deposition and gene expression

Data are presented as mean ± SEM; * p<0.05 vs Normoxia; # p<0.05 vs CH
Right ventricular autophagy

Data are presented as mean± SEM; * p<0.05 vs Normoxia; # p<0.05 vs CH
Ultrastructure evidence of autophagosome in the RV

Arrows: double-membrane autophagosome.
Conclusions

→ Phosphodiesterase-5 inhibitor prevents hypoxia-induced cardiopulmonary remodeling;

→ The intracellular degradation of collagen could be associated with the induction of autophagy.
Thank you for your attention