Ivabradine rescues vascular abnormalities in a mouse model of Duchenne muscular dystrophy

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Introduction

Duchenne muscular dystrophy (DMD) is a rare genetic disorder initiated by the absence of dystrophin and is primarily differentiated by skeletal muscle degeneration and cardiac dysfunction. More recent studies underlined the importance of vascular abnormalities such as augmented arterial stiffness and endothelial dysfunction in the progression of cardiac complications (1). Impaired vasculature results in the apoptosis of cardiomyocytes and fibrosis which in turn activates the renin-angiotensin-aldosterone system (Overexpression of ACE) (2). Ivabradine, a selective inhibitor of If channels in the heart improves adverse left ventricular remodelling and vascular dysfunction in various cardiovascular disease (Figure 2). However, whether ivabradine treatment could improve the vascular complications in DMD is largely unknown.

Methods

In this study, we examined the vascular abnormalities in both dystrophin and utrophin deficient (mdx-utr) mice, a severe and progressive animal model of DMD. Mice (4-6 weeks old) were subjected to ivabradine (10 mg/kg/day in drinking water) or vehicle treatments for 3 to 4 weeks. At the end of the treatment, aorta and lung tissue were collected to assess the vascular reactivity, employing wire myograph and angiotensin-converting enzyme (ACE) activity measurement respectively (Figure 1).

Results

We depict that similar to DMD patients, mdx-utr mice also exhibit vascular abnormalities and cardiac fibrosis. Ivabradine-treated mice demonstrated a significantly improved endothelium-dependent vasodilation (p=0.05) and decreased vascular stiffness compared to vehicle-treated mdx-utr mice (p=0.01) (Figure 3). In addition, lung ACE activity was significantly reduced in the treated mice in comparison to the control group (p<0.01) indicating less activation in the renin-angiotensin-aldosterone system, which can contribute to the progression of cardiac fibrosis and vascular dysfunction (Figure 4).

Conclusion

In conclusion, our study for the first time shows the beneficial effects of ivabradine on the progression of cardiac vascular complications in DMD and this may present a novel therapeutic approach.

Table 1. Animal Characteristics (Data are expressed as mean±d.)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Heart weight/Body weight</th>
<th>Heart weight</th>
<th>Lung weight</th>
<th>Body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>6.30±0.14</td>
<td>22.00±1.02</td>
<td>1000±50</td>
<td>40±0.02</td>
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<td>Iva-treated</td>
<td>6.02±0.06</td>
<td>21.50±1.23</td>
<td>987±50</td>
<td>39±0.02</td>
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References