Background: Present knowledge on the effects of recombinant human growth hormone (rHGH) on aging and lifespan are controversial. Clinical data indicate that norm or high levels of GH may accelerate aging and increase the risk of cardiovascular diseases. Very small embryonic-like stem cells (VSELs) are a population of developmentally early stem cells residing in adult tissues, which could have the potential role in aging and organ rejuvenation.

Objective: The aim of the study was to analyze the effect of rHGH treatment on VSELs.

Methods: Twenty five patients: GH-deficient (20), Turner Syndrome (3), Prader-Willi Syndrome (2), treated with GH, mean age 9.1±2.7 years, were included in the study. The mean GH dose was 0.27 μg/kg/week. Fasting peripheral blood samples were taken before the administration of GH, then two weeks, one month, three months and six months after it. Subsequently, we evaluated by employing FACS changes in the number of circulating in peripheral blood (PB) small CD133+/Lin-CD45+ VSELs and CD34+/Lin-CD45+ VSELs - that are precursors of long term repopulating hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs).

Results: We found that the administration of rHGH initially stimulated for a month an increase in number of VSELs circulating in PB, and subsequently the number of VSELs decreased (Fig 1-4). After six months of treatment the number of circulating in PB VSELs was lower as compared to baseline values. The increase in VSELs number paralleled with increase in number of circulating MSCs and EPCs, however two months shift has been observed in case of EPCs. Finally, the number of MSCs and EPCs become lower than before GH treatment.

Conclusions: The treatment with GH modulates the population of VSELs, MSCs and EPCs circulating in PB. Our data suggests that: 1. VSELs respond to GH treatment, and 2. since the therapy with GH modulates population of VSELs, therefore it could influence life span and organ rejuvenation. The authors have NOTHING TO DISCLOSE.

Abstract

The influence of recombinant human growth hormone treatment on very small embryonic/epiblast-like stem cells (VSELs)

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Statistical analysis:

- The statistical analysis was performed ANOVA with post-hoc Turkey test. P<0.05 was considered as statistically significant.

Results:

- We found that the administration of rHGH initially stimulated for a month an increase in number of VSELs circulating in PB, and subsequently the number of VSELs decreased (Fig 1-4). After six months of treatment the number of circulating in PB VSELs was lower as compared to baseline values.
- The increase in VSELs number paralleled with increase in number of circulating MSCs and EPCs, however two months shift has been observed in case of EPCs. Finally, the number of MSCs and EPCs become lower than before GH treatment.
- The changes in 34+/VSELs/34+/HSCs during rHGH treatment were significantly positive (Table 1).

Conclusions:

- The treatment with GH modulates the population of VSELs, MSCs and EPCs circulating in PB. Our data suggests that: 1. VSELs respond to GH treatment, and 2. since the therapy with GH modulates population of VSELs, therefore it could influence life span and organ rejuvenation. The authors have NOTHING TO DISCLOSE.

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Background:

Present knowledge on the effects of recombinant human growth hormone (rHGH) on aging and lifespan are controversial. Clinical data indicate that normal or high levels of GH may accelerate aging and increase the risk of cardiovascular diseases.

Methods:

Very small embryonic-like stem cells (VSELs) are a population of developmentally early stem cells residing in adult tissues (Ratafijczak MK et al. Aging 2012;4:235-246). These rare cells, which are slightly smaller than red blood cells,

- become mobilized during stress situations into peripheral blood,
- are enriched in the Sca1+/Lin-/CD45- cell fraction in mice and the CD133+/Lin-/CD45- cell fraction in humans,
- express markers of pluripotent stem cells (e.g., Oct4, Nanog, and SSEA), and
- display a distinct morphology characterized by a high nuclear/cytoplasmic ratio and undifferentiated chromatin.

The most recent data in vivo demonstrated that both murine and human VSELs exhibit some characteristics of long-term repopulating hematopoietic stem cells (LT-HSCs), are at the top of the hierarchy in the mesenchymal lineage, and may differentiate into organ-specific cells (e.g., cardiomyocytes). Moreover, as recently demonstrated the number of these cells positively correlates in several murine models with longevity. VSELs have the potential role in aging and organ rejuvenation and number of these cells decreases in experimental animals after prolonged GH or IGF-1 administration. (Kucia M et al. Age 2013;35:315-30).

Table 1. The mean number of VSELs, hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) per micro liter of blood.

<table>
<thead>
<tr>
<th></th>
<th>Before GH-therapy</th>
<th>After 2 weeks</th>
<th>After 1 month</th>
<th>After 3 months</th>
<th>After 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSELs</td>
<td>34+/VSELs</td>
<td>6.1±2.25</td>
<td>0.04±0.96</td>
<td>0.22±1.38</td>
<td>0.07±0.32</td>
</tr>
<tr>
<td>HSCs</td>
<td>153+/HSCs</td>
<td>8.90±1.43</td>
<td>0.87±0.84</td>
<td>0.18±1.09</td>
<td>0.08±0.04</td>
</tr>
<tr>
<td>MSCs</td>
<td>8.38±0.24</td>
<td>0.24±0.25</td>
<td>0.34±0.15</td>
<td>0.27±0.15</td>
<td>0.23±0.15</td>
</tr>
<tr>
<td>EPCs</td>
<td>6.25±0.25</td>
<td>0.32±0.25</td>
<td>0.21±0.16</td>
<td>0.16±0.13</td>
<td>0.28±0.24</td>
</tr>
</tbody>
</table>

Conclusions:

- The prolonged treatment with rHGH modulates the population of VSELs, MSCs and EPCs circulating in PB.
- Our data suggests that:
  1. VSELs respond to GH treatment, and
  2. since the therapy with GH modulates population of VSELs, therefore it could similarly as in experimental animals influence life span and organ rejuvenation in patients.

Acknowledgements

This study was supported by a grant “Harmonia” nr UM0-2014/14/MAN2/00473, from National Science Centre.