Self-reliant bioactive forms of vitamin B12

Technology

Vitamin B12 deficiency can originate due to poor nutrition or due to genetic mutations in genes that are essential for the utilization of this micronutrient in cells. Current chemical forms of vitamin B12 are unable to halt disease progression, i.e. neurological and hematological symptoms, in conditions that block this micronutrient utilization in humans. One case is the cblC genetic disease as well as other pathologies leading to B12-dependent homocystinuria and methylmalonic aciduria where B12 reaches the cells but it cannot be utilized. Herein, a new generation of B12 forms is presented, with the intrinsic property of bypassing intracellular enzymatic processing, undergoing self-activation in cells, and thus promising a superior therapeutic avenue for patients with the cblC disease and other forms of vitamin B12 deficiency. This new generation of B12 forms is expected to alleviate or correct vitamin B12 deficiencies associated with aging or with neurological impairments such as Alzheimer and Parkinson’s disease, where brain atrophy and cognitive decline are hallmarks.

Innovation

- Self-reliant bioactive forms of vitamin B12 that bypass intracellular enzymatic processing of the micronutrient

Application

- Newborns with a gene defect in the cblC (MMACHC) gene and other vitamin B12-dependent disorders leading to:
  - homocystinuria
  - methylmalonic aciduria
- Elderly people with latent, subclinical vitamin B12 deficiency
- Supportive treatment of Alzheimer’s and dementia patients
- Vegetarians and vegans

Developmental Status

- This new generation of self-reliant forms of vitamin B12 has been synthesized and isolated in pure form.
- Chemical reactivity with physiological reductants exhibited self-reliant activation
- The enzymatic activity of pathogenic variants of the cblC enzyme causing early and late disease onset in humans was restored to near normal levels
- Homocystinuria and methylmalonic aciduria where corrected in cblC patient cells

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Cobalamin Metabolism in Humans

Vitamin B12 deficiency can originate due to poor nutrition or due to genetic mutations in genes that are essential for the utilization of the micronutrient in cells. Current chemical forms of vitamin B12 are unable to halt disease progression, i.e., neurological and hematological symptoms, in conditions that block this micronutrient utilization in cells. One case is the cobic genetic disease as well as other pathologies leading to B12-dependent homocystinuria and methylnalonic aciduria where B12 reaches the cells but it cannot be utilized. Herein, a new generation of B12 forms is presented, with the intrinsic neurological and hematological symptoms, in conditions that block this micronutrient utilization in humans. One case is the condition of pure CyaCbl and MPGCbl.

4. Binding of CyaCbl and MPGCbl to human recombinant Cbl

5. Detrillation of MPGCbl by human recombinant Cbl

Table 2: Cytotoxic activity of human recombinant Cbl in the presence of new cobalamin derivatives as the substrate

<table>
<thead>
<tr>
<th>Cobalamin</th>
<th>MethylArg161Glu (nM)</th>
<th>MethylArg161Gln (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC1</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>HC1Cbl</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>HC1</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Me-S-MeCbl</td>
<td>7.5</td>
<td>11.5</td>
</tr>
<tr>
<td>GCbl</td>
<td>25</td>
<td>9.8</td>
</tr>
<tr>
<td>MPGCbl</td>
<td>&lt;1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Cytotoxicity of different cobalamin derivatives as a function of their concentration. The cytotoxicity was determined by MTT assay (n=3).

Concluding Remarks

A new generation of bioactive cobalamin derivatives featuring Co-S and Co-C axial coordination has been designed, synthesized and isolated in pure form.

The new Cbl derivatives bind to human recombinant CblC and show wild type and pathogenic variants, and undergo conversion to the base-off configuration, the primed form required for downstream catalysis.

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