Consequences of vitamin B12 deficiency in embryonic development and neonatal survival

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https://www.swansonvitamins.com/blog/health-news-and-opinion/vitamin-b12-foods
Vitamin B12 (cobalamin)

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Nielsen et al., 2012
Several populations are at risk for vitamin B12 deficiency

**Who’s at risk:**
- Decreased absorption
  - Older adults
  - Diseases involving malabsorption
- Low intake
  - Low and middle income nations
- Increased Need
  - Pregnant and nursing mothers

**Deficiency results in:**
- megaloblastic anemia
- Fatigue and weakness
- poor memory, depression
- peripheral neuropathy
- Risk factor for neural tube defects

[https://www.swansonvitamins.com/blog/health-news-and-opinion/vitamin-b12-foods](https://www.swansonvitamins.com/blog/health-news-and-opinion/vitamin-b12-foods)
Vitamin B12 is required for 2 essential processes:

1. **DNA**
   - 5-methyl TH-Folate
   - Methionine synthase (B12)
   - Purines, pyrimidines
   - TH-Folate
   - Methionine

2. **ENERGY**
   - Mitochondrion
   - Methylmalonyl-CoA
   - Methylmalonyl-CoA mutase (B12)
   - Succinyl-CoA
CD320 receptor functions to transport vitamin B12 from blood into tissues

Transcobalamin receptor (CD320)

Transcobalamin-bound Vitamin B12

Nielsen et al., 2012
Mice are used to model vitamin B12 deficiency
Vitamin B12 is required for 2 essential processes:

1. **DNA**
   - Methionine synthase (MTR KO) - no offspring

2. **ENERGY**
   - Methanol dehydrogenase (MUT KO) - offspring perish as newborns
Generate global $Cd320$ KO

Mice can survive without $Cd320$!
Are the *Cd320* KO mice deficient for vitamin B12?
Can we stress the KO mice with B12-deficient diet?

<table>
<thead>
<tr>
<th>Vitamin B12</th>
<th>Standard Diet</th>
<th>Soy Diet With vitamin B12</th>
<th>Soy Diet Vitamin B12-deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Blood vitamin B12 concentration after 12 weeks on diet
Blood MMA and homocysteine concentrations after 24 weeks on diet

Nielsen et al., 2012
Breeding mice on B12-deficient diet

Control

Vitamin B12 supplemented

Vitamin B12-deficient diet

Cd320 KO

0
Reproductive defect in one or both sexes?

$Cd320$ KO  
CONTROL

$Cd320$ KO  
CONTROL

0
Can vitamin B12 rescue the reproductive defect?

VB12 +

KO

KO

15 pups born – all died <24 hrs
Can vitamin B12 rescue the newborn lethality?

VB12 + C-section (E17.5)

VB12 +

15 pups born – 1 survived to weaning
Can vitamin B12 rescue the newborn lethality?

VB12 +
Progesterone +
C-section (E19.5)

KO
KO

VB12 +

17 pups born – 14 survived to weaning
Can vitamin B12 rescue the newborn lethality?

VB12 +
Progesterone +
C-section (E19.5)

KO KO

VB12 +
Saline +

15 pups born – 10 survived to weaning regardless of treatment
Bringing it back to humans

Meat Consumption per capita
- Less than 16.7
- 16.7 – 30
- 30 – 42.5
- 42.5 – 55.3
- 55.3 – 68.6
- 68.6 – 80.2
- 80.2 – 91.4
- 91.4 – 102
- 102 – 120.2
- No data

in kg per person
Year: 2009

http://chartsbin.com/view/12730
Looking at Development
Microphthalmia

LEFT: Normal

RIGHT: abnormal
Birth defects have been seen in some offspring

CONTROL

0

0/62

Cd320 KO

4/52
Conclusions

• Metabolic phenotype
  • Higher homocysteine
    • Specifically in female KO

• Reproductive defect
  • Perish early during embryonic development
  • Rescue development with vitamin B12 injection
  • Perish shortly after birth
  • May be rescued by vitamin B12 injection
Future Questions to Address
Future Journey

Johns Hopkins Center for American Indian Health

Hello, my name is Future M.D.
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