Leptin as a Survival Hormone:
Diet Restriction, Cognition & Longevity:
Relationship to Eating Disorders

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Lecture Outline: A three fold cord......

Leptin

Cognition

Longevity

Diet Restriction
Intake - Output

Leptin

Different effects of Diet Restriction – Undernutrition vs Malnutrition

<table>
<thead>
<tr>
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<th>Undernutrition Diet Restriction</th>
<th>Malnutrition</th>
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<tbody>
<tr>
<td>Quantity</td>
<td>Decreased</td>
<td>Decreased</td>
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<tr>
<td>Essential nutrients</td>
<td>NORMAL</td>
<td>Decreased</td>
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<tr>
<td>Longevity</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Cognitive Function</td>
<td>Increased</td>
<td>Decreased</td>
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Does anorexia occur in nature?
Only short-term starvation.
No animal will starve itself to death....

Hibernation - Bears
Migration - Birds, Whales, Turtles
Territorial Defense - Seals
Egg Incubation - Penguins (1), Octopus (200,000)

Clinical Cases of anorexia
Similar Weights, Different Responses

Patient 1
Restrictive Anorexia, admitted at weight of 26 kg
~ Diet Restriction

Patient 2
Social isolation & Depression
No school parties for 2 years
~ Separation

Patient 3
Hospitalized, ate diet but did not gain weight.
No evidence of vomiting ???
~ Activity

Diet Restriction increases survival in Mice

Weindruch, 1996 Sci Am

"Dose" Dependent
Cognition improved by DR to 60%, impaired by 40% DR: reversed by Tyrosine ... How come?

Identical reduction of Leptin levels despite different % Diet Restriction

DR to 60% (but not 40%) stimulates hippocampal OB-long receptor expression & signaling

Leptin reverses dose-dependent activation of Hippocampal AMPK (X6) following Diet Restriction
Diet restriction, Cognition & Longevity

Elliot Berry

Leptin (1 mg/kg) improves cognitive impairment following DR to 40%

Leptin reduces neuronal apoptosis (↓ Bax, ↑ Bcl-2) induced by 40% DR

Leptin increases survival in mice on DR to 40% without weight change

Leptin increases expression of SIRT-1 following experimental stroke

Over-expression of Sir2 extends life span of Drosophila

Leptin levels correlate with survival in Intensive Care patients

Leptin increases expression of SIRT-1 following experimental stroke

• Sirtuin protein family: Silent Information Regulator T1
• Homolog to the yeast & drosophila Sir2 protein
• Deacetylates proteins that regulate reaction to stressors, longevity
• Sirt-1 mediates CR in mice.
• Mechanism involves attenuation of apoptosis.

Over-expression of Sir2 extends life span of Drosophila

Helfand et al., PNAS, 2004

Leptin levels correlate with survival in Intensive Care patients

Neuman, Sviri, Avraham & Berry unpublished data
The Link between Caloric Restriction, Cognitive Function & Longevity

- In states of negative energy balance (Under AND Malnutrition), Leptin improves Cognition (via AMPK, Neuroprotection) & Longevity (via Sirtuins)
- LEPTIN acts as a SURVIVAL Hormone

Therapeutic implications for catabolic, weight loss states such as Cachexia, Cancer, HIV/AIDS, Malnutrition & Eating Disorders

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